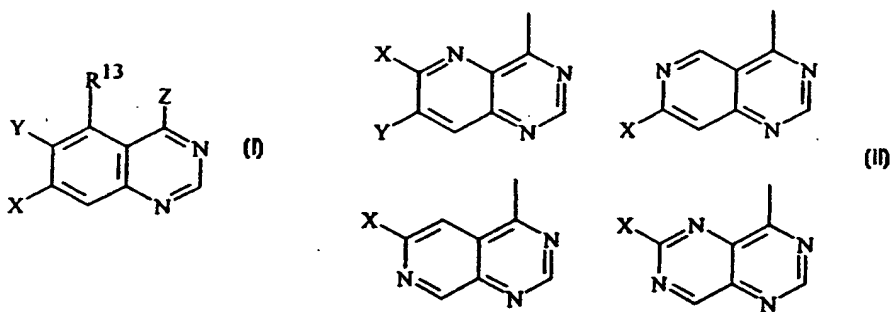




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 403/04, A61K 31/505, C07D 401/04, 413/14</b>		<b>A1</b>	(11) International Publication Number: <b>WO 99/06396</b>
			(43) International Publication Date: 11 February 1999 (11.02.99)
(21) International Application Number: PCT/US98/15592		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 29 July 1998 (29.07.98)			
(30) Priority Data: 60/054,061 29 July 1997 (29.07.97) US			
(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventor; and (75) Inventor/Applicant (for US only): BRIDGES, Alexander, James [GB/US]; 3301 Textile Road, Saline, MI 48176 (US).			
(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.			

(54) Title: IRREVERSIBLE BICYCLIC INHIBITORS OF TYROSINE KINASES



## (57) Abstract

The present invention provides compounds that are irreversible inhibitors of tyrosine kinases of formula (I) or (II). Also provided is a method of treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis and a pharmaceutical composition that comprises a compound that is an irreversible inhibitor of tyrosine kinases. In formulas (I) and (II), Z, X, Y or R<sup>13</sup> are as defined in the description.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## IRREVERSIBLE BICYCLIC INHIBITORS OF TYROSINE KINASES

## FIELD OF THE INVENTION

This invention relates to compounds that are irreversible inhibitors of tyrosine kinases. This invention also relates to a method of treating cancer, atherosclerosis, restenosis, endometriosis, and psoriasis, and to a pharmaceutical composition that comprises a compound that is an irreversible inhibitor of tyrosine kinases.

## BACKGROUND OF THE INVENTION

Cancer has been viewed as a disease of the intracellular signalling system, or signal transduction mechanism. Cells receive instructions from many extracellular sources, instructing them to either proliferate or not to proliferate. The purpose of the signal transduction system is to receive these and other signals at the cell surface, get them into the cell, and then pass the signals on to the nucleus, the cytoskeleton, and transport and protein synthesis machinery.

The most common cause of cancer is a series of defects, either in these proteins, when they are mutated, or in the regulation of the quantity of the protein in the cell such that it is over or under produced. Most often, there are key lesions in the cell which lead to a constitutive state whereby the cell nucleus receives a signal to proliferate, when this signal is not actually present. This can occur through a variety of mechanisms. Sometimes the cell may start to produce an authentic growth factor for its own receptors when it should not, the so-called autocrine loop mechanism. Mutations to the cell surface receptors, which usually signal into the cell by means of tyrosine kinases, can lead to activation of the kinase in the absence of ligand, and passing of a signal which is not really there. Alternatively, many surface kinases can be overexpressed on the cell surface leading to an inappropriately strong response to a weak signal. There are many levels inside the cell at which mutation or overexpression can lead to the same

-2-

spurious signal arising in the cell, and there are many other kinds of signalling defects involved in cancer. This invention touches upon cancers which are driven by the three mechanisms just described, and which involve cell surface receptors of the epidermal growth factor receptor tyrosine kinase family (EGFR). This family consists of the EGF receptor (also known as Erb-B1), the Erb-B2 receptor, and its constitutively active oncoprotein mutant Neu, the Erb-B3 receptor and the Erb-B4 receptor. Additionally, other biological processes driven through members of the EGF family of receptors can also be treated by compounds of the invention described below.

The EGFR has as its two most important ligands Epidermal Growth Factor (EGF) and Transforming Growth Factor alpha (TGF alpha). The receptors appear to have only minor functions in adult humans, but are apparently implicated in the disease process of a large portion of all cancers, especially colon and breast cancer. The closely related Erb-B2, Erb-B3, and Erb-B4 receptors have a family of Heregulins as their major ligands, and receptor overexpression and mutation have been unequivocally demonstrated as the major risk factor in poor prognosis breast cancer. Additionally, it has been demonstrated that all four of the members of this family of receptors can form heterodimeric signalling complexes with other members of the family, and that this can lead to synergistic transforming capacity if more than one member of the family is overexpressed in a malignancy. Overexpression of more than one family member has been shown to be relatively common in human malignancies.

In addition to cancer, restenosis is also a disease in which undesired cellular proliferation occurs. Restenosis involves the proliferation of vascular smooth muscle cells. Restenosis is a major clinical problem associated with coronary angioplasty and other medical procedures. Restenosis generally occurs within about 0 to 6 months in about 30% to 50% of patients who undergo balloon angioplasty to clear clogged coronary arteries in an effort to treat heart disease due to occluded arteries. The resulting restenosis causes substantial patient morbidity and health care expense.

The process of restenosis is initiated by injury of the blood vessel, including arteries and veins, with the subsequent release of thrombogenic,

-3-

vasoactive, and mitogenic factors. Endothelial and deep vessel injury leads to platelet aggregation, thrombus formation, inflammation, and activation of macrophages and smooth muscle cells. These events induce the production of and release of growth factors and cytokines, which in turn may promote their own synthesis and release from target cells. Thus, a self-perpetuating process involving growth factors such as EGF, platelet derived growth factor (PDGF) or fibroblast growth factor (FGFs) is initiated. Thus, it would be useful to have irreversible inhibitors of signal transduction pathways, particularly of tyrosine kinases like EGF, PDGF, FGF, or src tyrosine kinases.

The proliferative skin disease psoriasis has no good cure at present. It is often treated by anticancer agents such as methotrexate, which have very serious side effects, and which are not very effective at the toxicity limited doses which have to be used. It is believed that TGF alpha is the major growth factor overproduced in psoriasis, since 50% of transgenic mice which over express TGF alpha develop psoriasis. This suggests that a good inhibitor of EGFR signalling could be used as antipsoriatic agent, preferably, but not necessarily, by topical dosing.

It is especially advantageous to have irreversible tyrosine kinase inhibitors when compared to reversible inhibitors, because irreversible inhibitors can be used in prolonged suppression of the tyrosine kinase, limited only by the normal rate of receptor resynthesis, also called turnover.

Additional information on the role of src tyrosine kinases in biological processes relating to cancer and restenosis can be found in the following documents, which are all hereby incorporated by reference.

Benjamin C.W. and Jones D.A., Platelet-Derived Growth Factor Stimulates Growth Factor Receptor Binding Protein-2 Association With Src In Vascular Smooth Muscle Cells, *JBC*, 1994;269:30911-30916.

Kovalenko M., et al., Selective Platelet-Derived Growth Factor Receptor Kinase Blockers Reverse Cis-transformation, *Cancer Res*, 1994;54:6106-6114.

Schwartz R.S., et al., The Restenosis Paradigm Revisted: An Alternative Proposal for Cellular Mechanisms, *J Am Coll Cardiol*, 1992;20:1284-1293.

-4-

Libby P., et al., Cascade Model for Restenosis - A Special Case of Atherosclerosis Progression, *Circulation*, 1992;86:47-52.

Additional information on the role of EGF tyrosine kinases in biological processes relating to cancer and restenosis can be found in the following document  
5 which is hereby incorporated by reference.

Jonathan Blay and Morley D. Hollenberg, Heterologous Regulation Of EGF Receptor Function In Cultured Aortic Smooth Muscle Cells, *Eur J Pharmacol, Mol Pharmacol Sect*, 1989;172(1):1-7.

Information that shows that antibodies to EGF or EGFR show in vivo  
10 antitumor activity can be found in the following documents which are hereby incorporated by reference.

Modjtahedi H., Eccles S., Box G., Styles J., Dean C., Immunotherapy Of Human Tumour Xenografts Overexpressing The EGF Receptor With Rat Antibodies That Block Growth Factor-Receptor Interaction, *Br J Cancer*,  
15 1993;67:254-261.

Kurachi H., Morishige K.I., Amemiya K., Adachi H., Hirota K., Miyake A., Tanizawa O., Importance Of Transforming Growth Factor Alpha/Epidermal Growth Factor Receptor Autocrine Growth Mechanism In An Ovarian Cancer Cell Line In Vivo, *Cancer Res*, 1991;51:5956-5959.

Masui H., Moroyama T., Mendelsohn J., Mechanism Of Antitumor Activity In Mice For Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies With Different Isotypes, *Cancer Res*, 1986;46:5592-5598.

Rodeck U., Herlyn M., Herlyn D., Molthoff C., Atkinson B., Varello M., Stepkowski Z., Koprowski H., Tumor Growth Modulation By A Monoclonal  
25 Antibody To The Epidermal Growth Factor Receptor: Immunologically Mediated And Effector Cell-Independent Effects, *Cancer Res*, 1987;47:3692-3696.

Guan E., Zhou T., Wang J., Huang P., Tang W., Zhao M., Chen Y., Sun Y., Growth Inhibition Of Human Nasopharyngeal Carcinoma In Athymic Mice By Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies,  
30 *Internat J Cell Clon*, 1989;7:242-256.

Masui H., Kawamoto T., Sato J.D., Wolf B., Sato G., Mendelsohn J., Growth Inhibition Of Human Tumor Cells In Athymic Mice By Anti-Epidermal

-5-

Growth Factor Receptor Monoclonal Antibodies, *Cancer Res*,  
1984;44:1002-1007.

In addition, the following documents show the antitumor activity of protein  
tyrosine kinase inhibitors. The documents are hereby incorporated by reference.

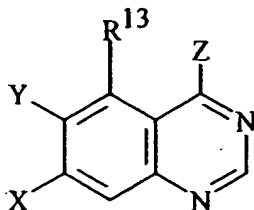
5           Buchdunger E., Trinks U., Mett H., Regenass U., Muller M., Meyer T.,  
McGlynn E., Pinna L.A., Traxler P., Lydon N.B., 4,5-Dianilinophthalimide: A  
Protein Tyrosine Kinase Inhibitor With Selectivity For The Epidermal Growth  
Factor Receptor Signal Transduction Pathway And Potent In Vivo Antitumor  
Activity, *Proc Natl Acad Sci USA*, 1994;91:2334-2338.

10           Buchdunger E., Mett H., Trinks U., Regenass U., Muller M., Meyer T.,  
Beilstein P., Wirz B., Schneider P., Traxler P., Lydon N., 4,5-Bis  
(4-Fluoroanilino)Phthalimide: A Selective Inhibitor Of The Epidermal Growth  
Factor Receptor Signal Transduction Pathway With Potent In Vivo Mdd  
Antitumor Activity, *Clinical Cancer Research*, 1995;1:813-821.

15           Compounds that are reversible inhibitors of tyrosine kinases have been  
described in US Patent Numbers 5,457,105, 5,475,001, and 5,409,930 and in PCT  
publication Numbers WO 9519774, WO 9519970, WO 9609294, and  
WO 9523141. The presently disclosed compounds, which are structurally different  
from the tyrosine kinase inhibitors described in the above-identified documents,  
20           are irreversible inhibitors of tyrosine kinases.

## SUMMARY OF THE INVENTION

The present invention provides compounds having the Formula I

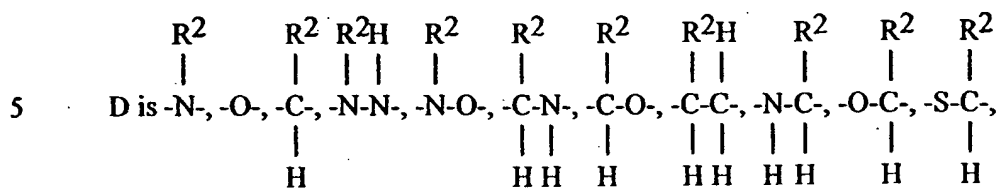


I

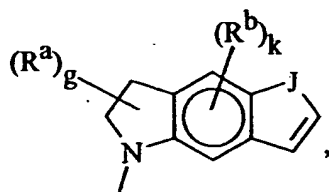
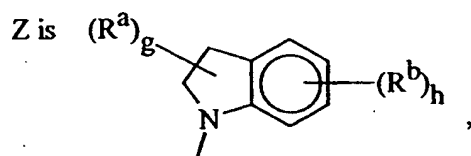
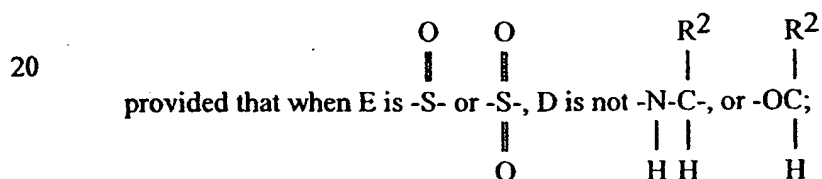
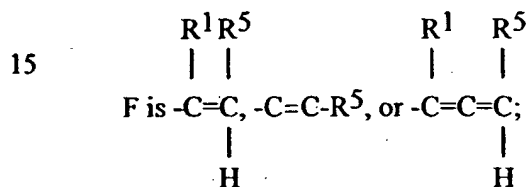
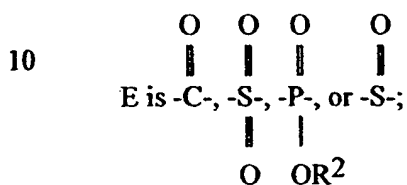
-6-

wherein X is -D-E-F and Y is -SR<sup>4</sup>, halogen, -OR<sup>4</sup>, -NHR<sup>3</sup>, or hydrogen, or X is

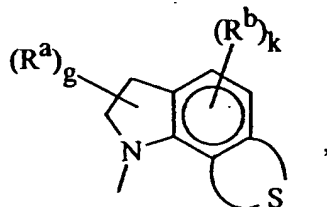
-SR<sup>4</sup>, halogen, -OR<sup>4</sup>, -NHR<sup>3</sup>, or hydrogen, and Y is -D-E-F;



or absent;

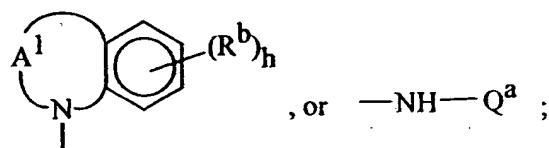
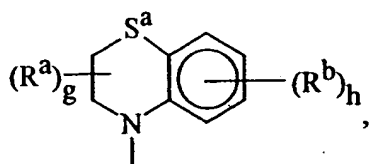
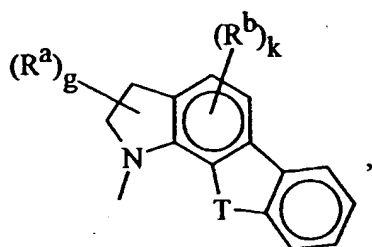


25





-7-



each  $R^a$  is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)

- 5                   alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not  
attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or  $R^a$  is  
independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)  
alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-  
(C<sub>1</sub>-C<sub>4</sub>)alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
10               4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

- each  $R^b$  is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy,  
amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy,  
benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl,  
15               (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino,  
trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl,  
N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino,  
trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or  
(C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said  
20               phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-

-8-

substituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R<sup>b</sup> is -Z<sup>a</sup>R<sup>77</sup>;

J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;

5 g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

10 T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;

S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

15 Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two  
20 substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],

25 -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the

-9-

A  
|

substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

5 -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

Z<sup>1</sup>, Z<sup>2</sup>, or Z<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub>

10 cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>, hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl, C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto, 15 C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxycarbonyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

Z<sup>a</sup> is a bond, -CH<sub>2</sub>-, -S-, SO<sub>2</sub>, -NH-, -O-, -OCH<sub>2</sub>-, -S-CH<sub>2</sub>-, -SO<sub>2</sub>CH<sub>2</sub>-, or -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub>

20 alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -C=CH<sub>2</sub>, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

25

|  
H

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to

-10-

three substituents independently selected from  $Z^1$ ,  $Z^2$ ,  $Z^3$  or a monocyclic heteroaryl group, and each  $C_1$ - $C_6$  alkyl group above in  $R^5$  can be substituted with  $-OH$ ,  $-NH_2$  or  $-NAB$ , where A and B are as defined above;

$R^{77}$  is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

$R^{13}$  is hydrogen or halogen; and

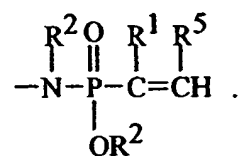
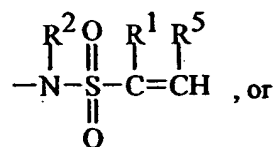
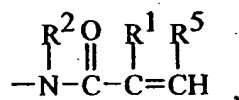
n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

In a preferred embodiment of the compounds of Formula I,

10 
$$\begin{array}{c} R^2 \quad O \quad CHR^5 \\ | \quad | \quad | \\ X - N - C - C - R^1, \text{ and } Y \text{ is hydrogen, or} \end{array}$$

15 
$$\begin{array}{c} R^2 \quad O \quad CHR^5 \\ | \quad | \quad | \\ X \text{ is hydrogen, and } Y - N - C - C - R^1. \end{array}$$

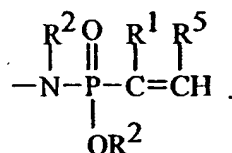
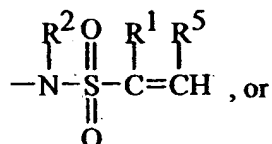
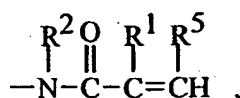
In another preferred embodiment of the compounds of Formula I, Y is  $-D-E-F$ , and  $-D-E-F$  is



In another preferred embodiment of the compounds of Formula I, X is

20  $-D-E-F$ , and  $-D-E-F$  is

-11-



In another preferred embodiment of the compounds of Formula I, R<sup>2</sup> is hydrogen.

5 In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O(CH<sub>2</sub>)<sub>n</sub>-morpholino.

In another preferred embodiment of the compounds of Formula I, R<sup>5</sup> is carboxy, (C<sub>1</sub>-C<sub>6</sub> alkyl)oxycarbonyl or C<sub>1</sub>-C<sub>6</sub> alkyl.

In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O(CH<sub>2</sub>)<sub>n</sub>morpholino.

10 In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl].

In another preferred embodiment of the compounds of Formula I, Y is -D-E-F and X is -O-(CH<sub>2</sub>)<sub>n</sub>-imidazolyl.

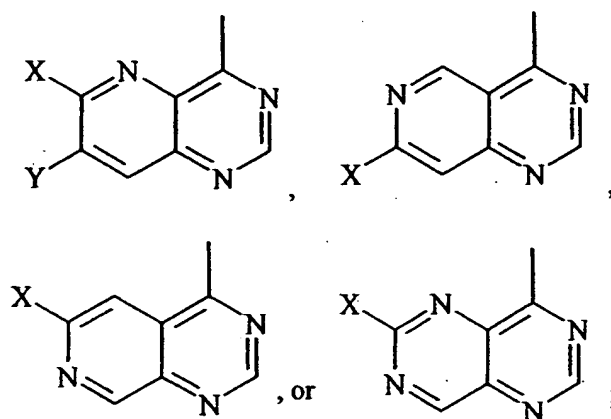
15 In another embodiment, the present invention provides compounds having the Formula II

Q-Z

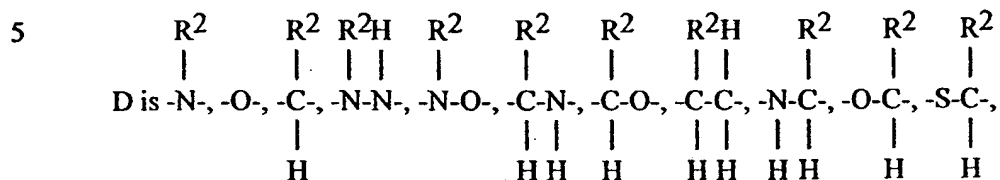
II

wherein Q is

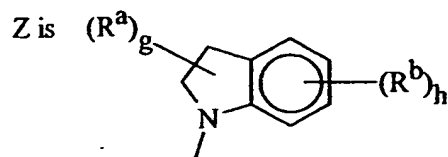
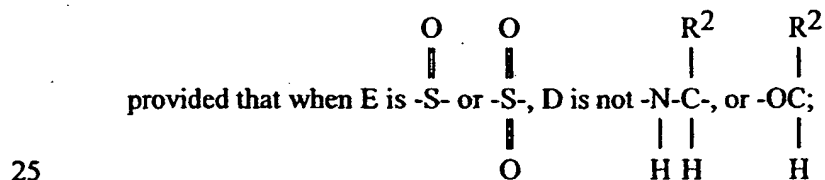
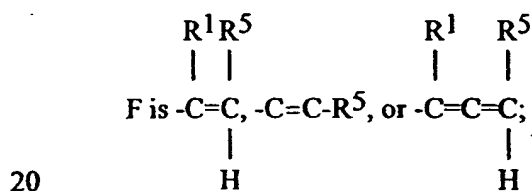
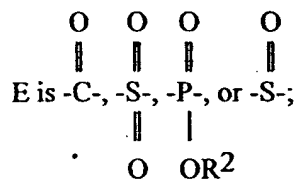
-12-



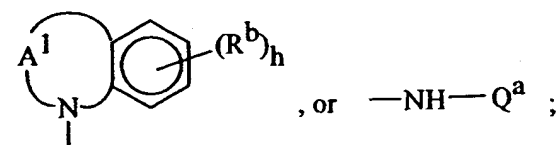
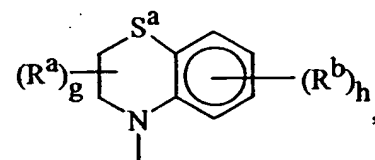
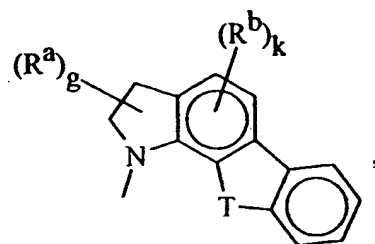
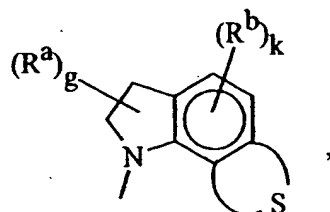
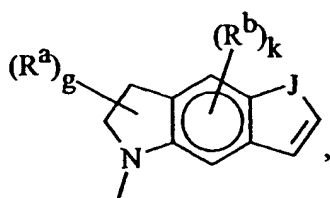
p is 0 or 1;

X is -D-E-F and Y is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, or X is -SR<sup>4</sup>, -OR<sup>4</sup>,-NHR<sup>3</sup> or hydrogen, and Y is -D-E-F;

10 or absent;



-13-



5

each  $R^a$  is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)

alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not

attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or  $R^a$  is

independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)

10

alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-

(C<sub>1</sub>-C<sub>4</sub>)alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl,

4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl,

(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

-14-

- each  $R^b$  is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano,  $(C_1-C_4)$ alkyl, phenyl, thienyl,  $(C_1-C_4)$ alkoxy, benzyloxy, phenoxy,  $(C_2-C_6)$ alkenyl,  $(C_2-C_6)$ alkynyl,  $(C_1-C_4)$ alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino,  $(C_1-C_4)$ alkanoylamino,  $(C_1-C_4)$ alkanoyl, N-mono- or N,N-di- $(C_1-C_4)$ alkylamino,  $(C_1-C_4)$ alkylsulfonylamino, trifluoromethylsulfonylamino,  $(C_1-C_4)$ alkylthio,  $(C_1-C_4)$ alkylsulfinyl or  $(C_1-C_4)$ alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy, or  $(C_1-C_4)$ alkyl and said  $(C_1-C_4)$ alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or  $R^b$  is  $-ZaR^{77}$ ;
- J is  $-CH_2-$ , thio,  $-N(H)-$ , or oxy;
- g is 0, 1, or 2;
- h is 0 to 4;
- k is 0, 1, or 2;
- S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;
- T is  $-CH_2-$ ,  $-N(H)-$ , thio, or oxy;
- $S^a$  is  $-CH_2-$ , oxy, or thio;
- $A^1$  completes a 7- to 9-membered mono-unsaturated mono-aza ring;
- $Q^a$  is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or  $Q^a$  is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl,



(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

$R^1$  is hydrogen, halogen, or  $C_1$ - $C_6$  alkyl;

**R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,**

5  $-(CH_2)_n$ -N-piperazinyl,  $-(CH_2)_n$ -N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],  
 $-(CH_2)_n$ -N-pyrrolidyl,  $-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n$ -N-imidazolyl,  
 $-(CH_2)_n$ -imidazolyl,  $-(CH_2)_n$ -N-morpholino,  $-(CH_2)_n$ -N-thiomorpholino,  
 $-(CH_2)_n$ -N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the

10. substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are  
independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,  
-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,  
-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,  
15 -(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

E<sup>1</sup>, E<sup>2</sup>, or E<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>, hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl, C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxycarbonyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

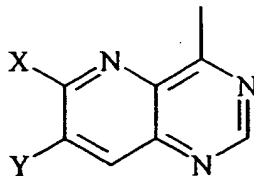
25       $Z^a$  is a bond,  $-CH_2-$ ,  $-S-$ ,  $SO_2$ ,  $-NH-$ ,  $-O-$ ,  $-OCH_2-$ ,  $-S-CH_2-$ ,  $-SO_2-$ , or  $-CH_2CH_2-$ ;

**R<sup>77</sup> is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;**

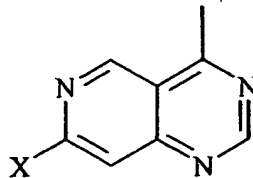
-16-

- $R^5$  is hydrogen, halogen,  $C_1$ - $C_6$  perfluoroalkyl, 1,1-difluoro( $C_1$ - $C_6$ )alkyl,  $C_1$ - $C_6$  alkyl,  $-(CH_2)_n$ -N-piperidinyl,  $-(CH_2)_n$ -piperazinyl,  $-(CH_2)_n$ -piperazinyl[ $N_4$ -( $C_1$ - $C_6$ )alkyl],  $-(CH_2)_n$ -N-pyrrolidyl,  $-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n$ -N-imidazolyl,  $-(CH_2)_n$ -N-morpholino,  $-(CH_2)_n$ -N-thiomorpholino,  $-C=CH_2$ ,  $-CH=CH-(C_1-C_6)alkyl$ ,  
 5  
 $\begin{array}{c} | \\ H \end{array}$   
 $-(CH_2)_n$ -N-hexahydroazepine,  $-(CH_2)_nNH_2$ ,  $-(CH_2)_nNH(C_1-C_6)alkyl$ ,  $-(CH_2)_nN(C_1-C_6)alkyl)_2$ , -1-oxo( $C_1-C_6$ )alkyl, carboxy,  
 10  
 $(C_1-C_6)alkyloxycarbonyl$ ,  $N-(C_1-C_6)alkylcarbamoyl$ , phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from  $E^1$ ,  $E^2$ ,  $E^3$  or a monocyclic heteroaryl group, and each  $C_1$ - $C_6$  alkyl group can be substituted with -OH, -NH<sub>2</sub> or -NAB, where A and B are as defined above; and  
 15  
 n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

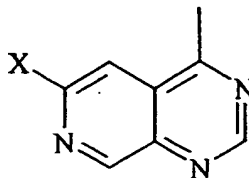
In another preferred embodiment of the compounds of Formula II, Q is



In another preferred embodiment of the compounds of Formula II, Q is

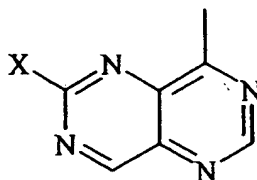


In another preferred embodiment of the compounds of Formula II, Q is

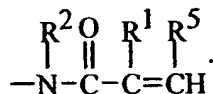


-17-

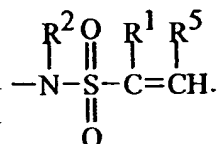
In another preferred embodiment of the compounds of Formula II, Q is



In another preferred embodiment of the compounds of Formula II, X is



5 In another preferred embodiment of the compounds of Formula II, X is

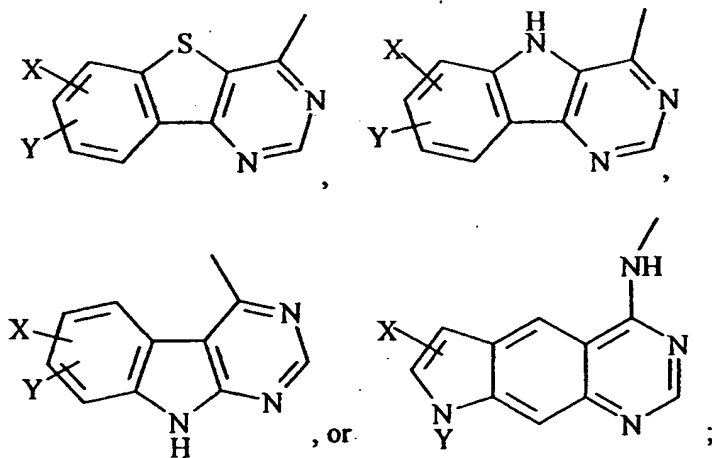


In another embodiment, the present invention provides compounds having the Formula II

Q-Z

II

10 wherein Q is

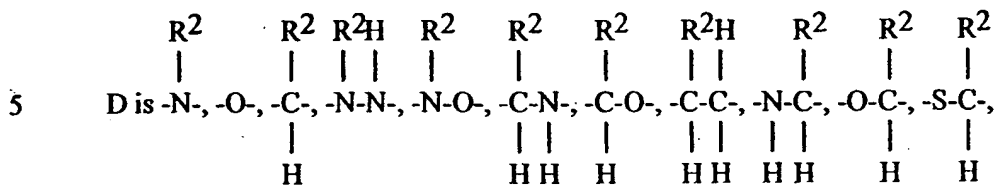


p is 0 or 1;

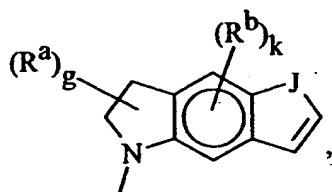
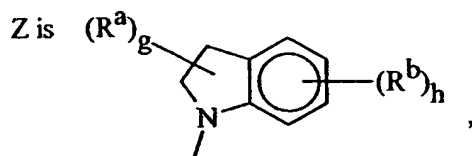
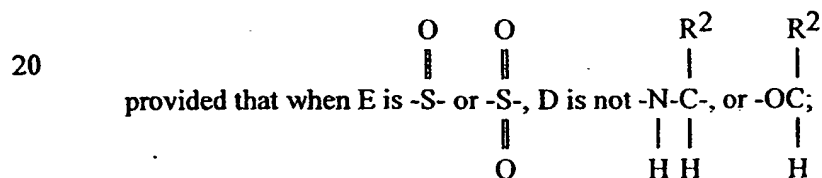
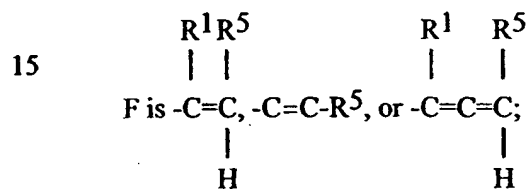
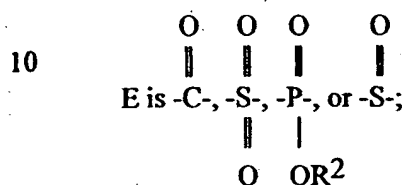
-18-

X is -D-E-F, and Y is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, or X is -SR<sup>4</sup>, -OR<sup>4</sup>,

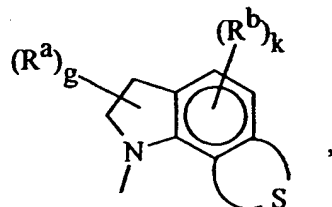
-NHR<sup>3</sup> or hydrogen, and Y is -D-E-F;



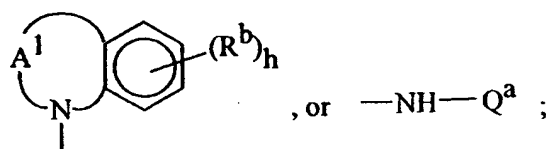
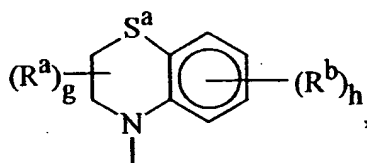
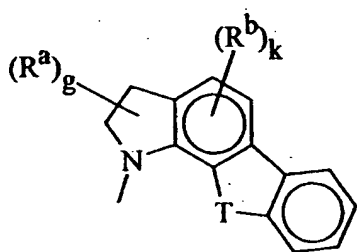
or absent;



25



-19-



each  $R^a$  is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)

- 5           alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not  
attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or  $R^a$  is  
independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)  
alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-  
(C<sub>1</sub>-C<sub>4</sub>)alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
10       4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

- each  $R^b$  is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy,  
amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy,  
benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl,  
15       (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino,  
trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl,  
N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino,  
trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or  
(C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said  
20       phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-

-20-

substituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R<sup>b</sup> is -Z<sup>a</sup>R<sup>77</sup>;

J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;

5 g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

10 T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;

S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],

25 -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the

-21-

A

|

substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are

independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

5 -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

E<sup>1</sup>, E<sup>2</sup>, or E<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub>

cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub>

10 perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl),

-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>,

hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl,

C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl,

C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto,

15 C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxycarbonyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,

C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

Z<sup>a</sup> is a bond, -CH<sub>2</sub>-, -S-, SO<sub>2</sub>, -NH-, -O-, -OCH<sub>2</sub>-, -S-CH<sub>2</sub>-, -SO<sub>2</sub>-, or

-CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>77</sup> is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted

20 heterocyclic aromatic ring;

R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub>

alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino,

25 -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -C=CH<sub>2</sub>, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

|  
H

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>)alkyl),

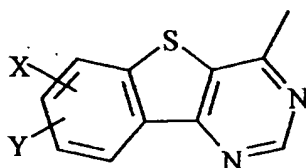
-(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>, -l-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy,

-22-

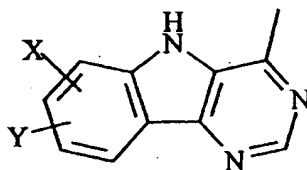
(C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbonyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from E<sup>1</sup>, E<sup>2</sup>, E<sup>3</sup> or a monocyclic heteroaryl group, and each C<sub>1</sub>-C<sub>6</sub> alkyl group can be substituted with -OH, -NH<sub>2</sub> or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

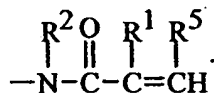
In another preferred embodiment of the compounds of Formula III, Q is



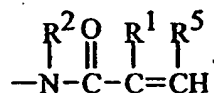
In another preferred embodiment of the compounds of Formula III, Q is



In another preferred embodiment of the compounds of Formula III, X is



In another preferred embodiment of the compounds of Formula III, X is



In another preferred embodiment, Q is a 6-substituted benzothieno[3,2-d]pyrimidin-4-yl.

The present invention also provides a pharmaceutically acceptable composition that comprises a compound of Formula I or II.

The present invention also provides a method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Formula I or II.



-23-

The present invention also provides a method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis, a therapeutically effective amount of a compound of Formula I or II.

5       The present invention also provides a method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Formula I or II.

10       The present invention also provides a method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Formula I or II.

      The present invention also provides a method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Formula I or II.

15       The present invention also provides a method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient in need of tyrosine kinase inhibition a tyrosine kinase inhibiting amount of a compound of Formula I or II.

      In a most preferred embodiment the present invention provides the following compounds:

20       N-[4-(6-Bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;  
      N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;  
      N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]acrylamide;  
      N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylamide;  
      N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]acrylamide;  
25       N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]propynamide;  
      N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]propynamide;  
      N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]propynamide;  
      N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]propynamide;  
30       N-[4-(4-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-  
ynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

5 N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-  
dienamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-  
2-enamide;

10 N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-2-  
enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacryl-  
amide;

N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacrylamide;

15 6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)quinazoline;

6-(S-Vinylsulfonamido)-4-(6-pyrrol-1-yl-2,3-dihydroindol-1-  
yl)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-  
yl)quinazolin-6-yl]acrylamide;

20 N-[4-(6-Pyrrol-1-yl-2,3-dihydroindol-1-yl)-7-[4-(N,N-dimethylamino)  
butoxy]quinazolin-6-yl]acrylamide

N-[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-  
yl)quinazolin-6-yl]acrylamide;

25 N-[4-(Octahydroindol-1-yl)-7-[3-(4-morpholino)propoxy]quinazolin-6-  
yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-  
enamide;

N-[4-(Octahydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

30 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-hydroxy-4-  
oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-  
hydroxy-4-oxobut-2-enamide;

-25-

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

5 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

10 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

15 N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

20 N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

25 Pent-2-enedioic acid 1 {[4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1 {[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

30 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(5-Methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(5-methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

5 4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]amide;

10 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2,3,4,5-Tetrahydro-1H-benzoazepin-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

15 N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

20 N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

25 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

30 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

-27-

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

5 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

10 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimidine;

15 6-(S-Vinylsulfonamido)-4-(2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl)pyrido[3,4-d]pyrimidine;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

20 N-[4-(2,3,6,7,8,9-Hexahydro-1H-benzo[g]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

25 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

30 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

5 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

10 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

15 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(2,3-dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

20 Pent-2-enedioic acid 1 {[4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

25 7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

30 4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

5 [4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(2,3,5,6-Tetrahydropyrrolo[2,3-f]indol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

10 [7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylate;

[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

15 [4-(6-Ethynyl-2,3-dihydroindol-1-yl)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

20 N-(3-(4-Morpholino)propylamino)-4,O-[4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

25 Pent-2-enedioic acid 1 {[4-(6-methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1 {[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

30 [4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

[4-(6-Fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

- 7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;
- 7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-7-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;
- 5 4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;
- 4-Morpholin-4-ylbut-2-ynoic acid [4-(6-ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;
- 10 N-[4-(Quinol-2-ylamino)quinazolin-6-yl]acrylamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]acrylamide;
- N-[4-(Quinol-2-ylamino)quinazolin-7-yl]acrylamide;
- N-[4-(Indol-5-ylamino)quinazolin-7-yl]acrylamide;
- N-[4-(Quinol-3-ylamino)quinazolin-6-yl]propynamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]propynamide;
- 15 N-[4-(Quinol-3-ylamino)quinazolin-7-yl]propynamide;
- N-[4-(Indol-5-ylamino)quinazolin-7-yl]propynamide;
- N-[4-(Quinol-5-ylamino)quinazolin-6-yl]but-2-ynamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-ynamide;
- N-[4-(Quinol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;
- 20 N-[4-(Indol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;
- N-[4-(Quinol-6-ylamino)quinazolin-6-yl]but-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-enamide;
- N-[4-(Quinol-6-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;
- 25 N-[4-(Quinol-7-ylamino)quinazolin-6-yl]-3-chloroacrylamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-3-chloroacrylamide;
- 6-(S-Vinylsulfonamido)-4-(quinol-7-ylamino)quinazoline;
- 6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)quinazoline;
- N-[7-[3-(4-Morpholino)propoxy]-4-(quinol-8-ylamino)quinazolin-6-yl]acrylamide;
- 30 N-[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylamide;



-31-

- N-[7-[4-(N,N-dimethylamino)butoxy]-4-(quinol-8-ylamino)quinazolin-6-yl]acrylamide;
- N-[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylamide;
- 5 N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;
- N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;
- 10 N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;
- N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;
- 15 N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;
- N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;
- 20 N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;
- 25 N-[4-(Indol-6-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;
- 30 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-6-ylamino)quinazolin-6-yl]amide;
- 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;

-32-

- Pent-2-enedioic acid 1 {[4-(indol-5-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];
- Pent-2-enedioic acid 1 {[4-(1H-indazol-6-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];
- 5 N-[4-(1H-Indazol-6-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;
- N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;
- 7-Morpholin-4-ylhept-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl]amide;
- 10 7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;
- 4-Morpholin-4-ylbut-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl] amide;
- 15 4-Morpholin-4-ylbut-2-ynoic acid [4-(4-benzyloxyphenylamino)quinazolin-6-yl]amide;
- N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;
- N-[4-(1H-Indazol-4-ylamino)pyrido[4,3-d]pyrimid-7-yl]acrylamide;
- 20 N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;
- N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;
- N-[4-(1H-Benzotriazol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;
- 25 N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;
- N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid -6-yl]but-2-ynamide;
- N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-
- 30 dienamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

-33-

- N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;
- N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-
- 5 4,4,4-trifluorobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;
- N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;
- 10 N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;
- 6-(S-Vinylsulfonamido)-4-(benzothiazol-5-ylamino)pyrido[3,4-d]-pyrimidine;
- 6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)pyrido[3,4-d]pyrimidine;
- N-[4-(Benzothiazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-
- 15 enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;
- N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-
- 20 enamide;
- N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;
- 25 N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;
- N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-
- 30 dimethylamino)propylamino)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

-34-

- N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;
- 5 N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;
- 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- 10 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- Pent-2-enedioic acid 1 {[4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];
- 15 Pent-2-enedioic acid 1 {[4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];
- N-[4-(1,2,3,4-Tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;
- N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;
- 20 7-Morpholin-4-ylhept-2-ynoic acid [4-(1,2,3,4-tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- 7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- 25 4-Morpholin-4-ylbut-2-ynoic acid [4-(benzo[c][2,1,3]thiadiazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- 4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- N-[4-(Benzo[c][2,1,3]thiadiazol-4-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;
- 30 N-[4-(Indol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;
- [4-(Benzimidazol-5-ylamino)quinazolin-6-yl]acrylate;

-35-

- [4-(Indol-5-ylamino)quinazolin-6-yl]acrylate;  
[4-(Benzimidazol-5-ylamino)quinazolin-7-yl]acrylate;  
[4-(Indol-5-ylamino)quinazolin-7-yl]acrylate;  
[7-[3-(4-Morpholino)propoxy]-4-(benzimidazol-5-ylamino)quinazolin-6-yl] acrylate;  
[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylate;  
[7-[4-(N,N-dimethylamino)butoxy]-4-(6-methoxyquinol-8-ylamino)quinazolin-6-yl]acrylate;  
[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylate;  
N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-methoxyquinol-8-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;  
N-(3-(4-Morpholino)propylamino)-4,O-[4-(indol-5-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;  
4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1-methylindol-5-ylamino)quinazolin-6-yl]ester;  
4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;  
Pent-2-enedioic acid 1 {[4-(indol-5-ylamino)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];  
Pent-2-enedioic acid 1 {[4-(1-methylindol-5-ylamino)quinazolin-6-yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];  
[4-(2-Methylindol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;  
[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;  
7-Morpholin-4-ylhept-2-ynoic acid [4-(3-cyanoindol-5-ylamino)quinazolin-6-yl]ester;  
7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;

- 4-Morpholin-4-ylbut-2-ynoic acid [4-(benzothien-5-ylamino)quinazolin-6-yl]ester;
- 4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]ester;
- 5 N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]acrylamide;
- N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]acrylamide;
- N-[4-(1-Benzylindol-5-ylamino)quinazolin-7-yl]acrylamide;
- N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-7-yl]acrylamide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]propynamide;
- 10 N-[4-(1-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]propynamide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-yl]propynamide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-yl]propynamide;
- N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]but-2-ynamide;
- N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]buta-2,3-
- 15 dienamide;
- N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]but-2-enamide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4,4,4-
- trifluorobut-2-enamide;
- N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-
- 20 enamide;
- N-[4-(1-Benzylindol-6-ylamino)quinazolin-6-yl]-3-chloroacrylamide;
- 6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)quinazoline;
- N-[7-[3-(4-Morpholino)propoxy]-4-(2-benzylbenzindazol-5-
- ylamino)quinazolin-6-yl]acrylamide;
- 25 N-[4-(1-Benzylindol-6-ylamino)-7-[4-(N,N-dimethylamino)butoxy]-
- quinazolin-6-yl]acrylamide;
- N-[4-(2-Phenylbenzimidazol-5-ylamino)-7-[3-(4-morpholino)propoxy]-
- quinazolin-6-yl]acrylamide;
- N-[4-(2-Phenylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-
- 30 enamide;
- N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-
- oxobut-2-enamide;

N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

5 N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

10 N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(42-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

15 N-[4-(2-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

20 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];

25 N-[4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

30 7-Morpholin-4-ylhept-2-ynoic acid [4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(3-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

5 N-[4-(3-Benzylbenzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

10 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

15 N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

20 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(1-phenethylbenzindazol-5-ylamino)-pyrido[3,4-d]pyrimidine;

25 6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)-pyrido[3,4-d]pyrimidine;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

30 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(2-Benzoyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;



-39-

- N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;
- 5 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;
- 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-10 5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];
- Pent-2-enedioic acid 1 {[4-(2-benzylsulfonylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl] amide} 5-[(3-morpholin-4-ylpropyl)amide];
- 15 N-[4-(4-benzylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;
- 7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-20 ylamino)pyrido[3,4-d]pyrimid-6-yl] amide;
- 7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylsulfonylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;
- N-[4-(2-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;
- 25 N-[4-(1-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;
- [4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylate;
- N-(3-(4-Morpholino)propylamino)-4-O-[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;
- 30 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester;

-40-

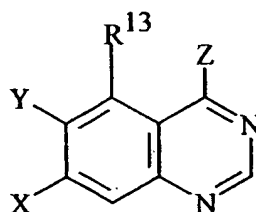
Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate; and

5 7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester.

### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds having the Formula I



10 wherein X is -D-E-F and Y is -SR<sup>4</sup>, halogen, -OR<sup>4</sup>, -NHR<sup>3</sup>, or hydrogen, or X is -SR<sup>4</sup>, halogen, -OR<sup>4</sup>, -NHR<sup>3</sup>, or hydrogen, and Y is -D-E-F;

15 D is -N-, -O-, -C-, -N-N-, -N-O-, -C-N-, -C-O-, -C-C-, -N-C-, -O-C-, -S-C-,  
 $\begin{array}{cccccccccccc} \text{R}^2 & \text{R}^2 & \text{R}^2\text{H} & \text{R}^2 & \text{R}^2 & \text{R}^2 & \text{R}^2\text{H} & \text{R}^2 & \text{R}^2 & \text{R}^2 \\ | & | & | & | & | & | & | & | & | & | \\ \text{H} & & & \text{H} & \text{H} & \text{H} & \text{H} & \text{H} & \text{H} & \text{H} \end{array}$

or absent;

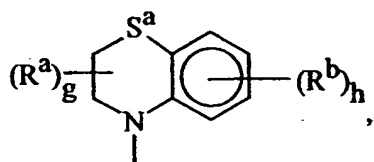
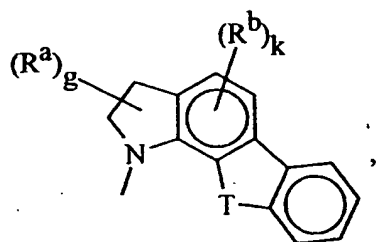
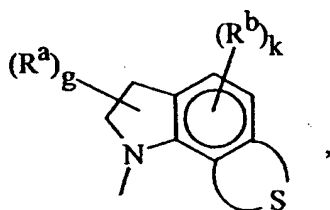
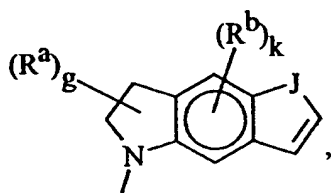
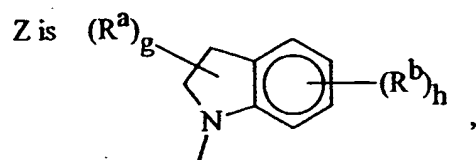
20 E is -C-, -S-, -P-, or -S-;  
 $\begin{array}{cccc} \text{O} & \text{O} & \text{O} & \text{O} \\ | & | & | & | \\ \text{O} & \text{OR}^2 & & \end{array}$

25 F is -C=C-, -C=C-R<sup>5</sup>, or -C=C=C-;  
 $\begin{array}{cc} \text{R}^1\text{R}^5 & \text{R}^1 & \text{R}^5 \\ | & | & | \\ \text{H} & & \text{H} \end{array}$

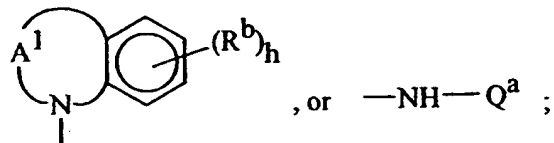
-41-

provided that when E is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \end{array}$  or  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \\ \parallel \\ \text{O} \end{array}$ , D is not  $\begin{array}{c} \text{R}^2 \\ | \\ \text{-N-C-} \\ | \quad | \\ \text{H} \quad \text{H} \end{array}$ , or  $\begin{array}{c} \text{R}^2 \\ | \\ \text{-OC-} \\ | \\ \text{H} \end{array}$ ;

5



10



-42-

- each R<sup>a</sup> is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>) alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R<sup>a</sup> is independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>) alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>)alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl, 4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- each R<sup>b</sup> is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy, amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino, trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-substituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R<sup>b</sup> is -Z<sup>a</sup>R<sup>77</sup>;
- J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;
- g is 0, 1, or 2;
- h is 0 to 4;
- k is 0, 1, or 2;
- S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;
- T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;
- S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

-43-

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen

5 and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, 10 di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],

-(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,

15 -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the

A  
|

substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are

20 independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

Z<sup>1</sup>, Z<sup>2</sup>, or Z<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub>

25 cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>, hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl,

-44-

C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl,  
 C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto,  
 C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxycarbonyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,  
 C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

5     Z<sup>a</sup> is a bond, -CH<sub>2</sub>-, -S-, SO<sub>2</sub>-, -NH-, -O-, -OCH<sub>2</sub>-, -S-CH<sub>2</sub>-, -SO<sub>2</sub>-, or  
       -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>77</sup> is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted  
       heterocyclic aromatic ring;

10     R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub>  
       alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl,  
       -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,  
       -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino,  
       -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -C=CH<sub>2</sub>, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
       15                                 |  
   H  
       -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl),  
       -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy,  
       (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbonyl, phenyl or  
       substituted phenyl, wherein the substituted phenyl can have from one to  
       20     three substituents independently selected from Z<sup>1</sup>, Z<sup>2</sup>, Z<sup>3</sup> or a monocyclic  
       heteroaryl group, and each C<sub>1</sub>-C<sub>6</sub> alkyl group can be substituted with -OH,  
       -NH<sub>2</sub> or -NAB, where A and B are as defined above, R<sup>6</sup> is hydrogen or  
       C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>13</sup> is hydrogen or halogen; and

25     n is 1 to 4, p is 0 or 1, and the pharmaceutically acceptable salts, esters, amides,  
       and prodrugs thereof.

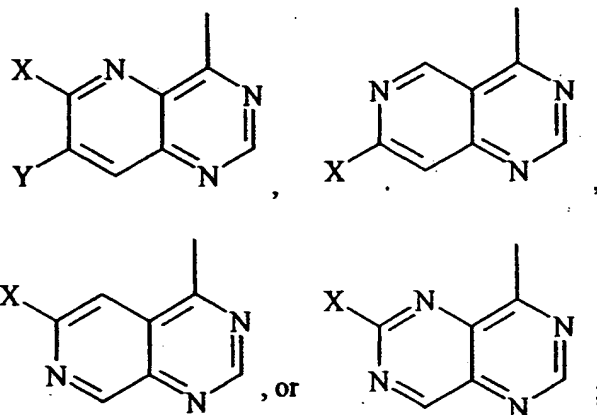
In another preferred embodiment, present invention also provides  
 compounds having the Formula II

Q-Z

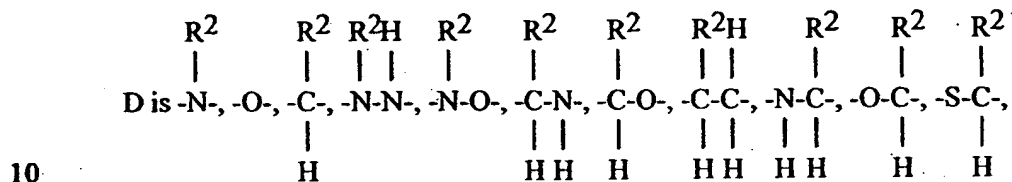
II

-45-

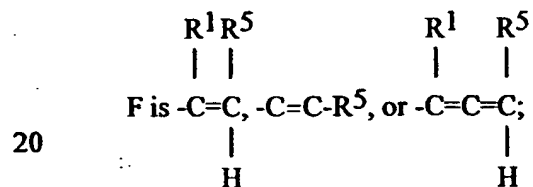
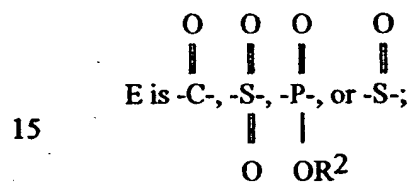
wherein Q is



p is 0 or 1;

X is -D-E-F, and Y is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, or X is -SR<sup>4</sup>, -OR<sup>4</sup>,5 -NHR<sup>3</sup> or hydrogen, and Y is -D-E-F;

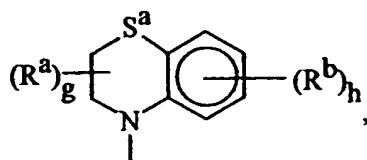
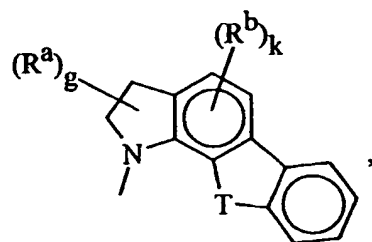
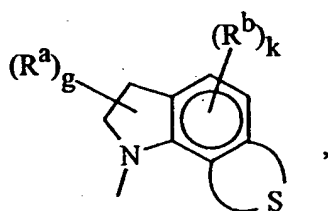
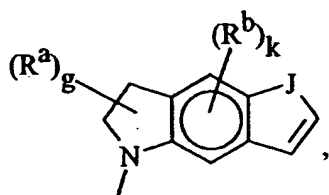
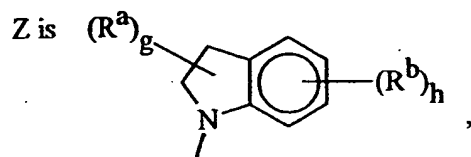
or absent;



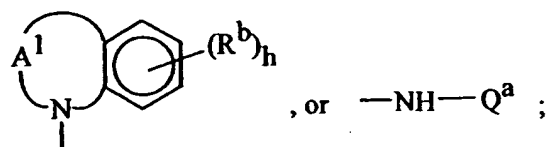
-46-

provided that when E is -S- or -S-, D is not -N-C-, or -OC;

5



10





each R<sup>a</sup> is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)

alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not

attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R<sup>a</sup> is

independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)

5 alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-

(C<sub>1</sub>-C<sub>4</sub>)alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl,

4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl,

(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>b</sup> is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy,

10 amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy,

benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl,

(C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino,

trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl,

N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino,

15 trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or

(C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said

phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-

substituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and

said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on

20 the benzene moiety, or R<sup>b</sup> is -Z<sup>a</sup>R<sup>77</sup>;

J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

25 S completes a 5- or 6-membered aromatic or partially saturated ring that can  
contain an oxygen or sulfur atom;

T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;

S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the

A  
|

substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are

independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

E<sup>1</sup>, E<sup>2</sup>, or E<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>, hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl,

-49-

C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl,  
 C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto,  
 C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy carbonyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,  
 C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

5 Z<sup>a</sup> is a bond, -CH<sub>2</sub>-, -S-, SO<sub>2</sub>-, -NH-, -O-, -OCH<sub>2</sub>-, -S-CH<sub>2</sub>-, -SO<sub>2</sub>-, or  
 -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>77</sup> is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted  
 heterocyclic aromatic ring;

10 R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub>  
 alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino,  
 -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -C=CH<sub>2</sub>, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 15  $\begin{array}{c} | \\ \text{H} \end{array}$   
 -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl),  
 -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy,  
 (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, phenyl or  
 substituted phenyl, wherein the substituted phenyl can have from one to  
 20 three substituents independently selected from E<sup>1</sup>, E<sup>2</sup>, E<sup>3</sup> or a monocyclic  
 heteroaryl group, and each C<sub>1</sub>-C<sub>6</sub> alkyl group can be substituted with -OH,  
 -NH<sub>2</sub> or -NAB, where A and B are as defined above or C<sub>1</sub>-C<sub>6</sub> alkyl; and  
 n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs  
 thereof.

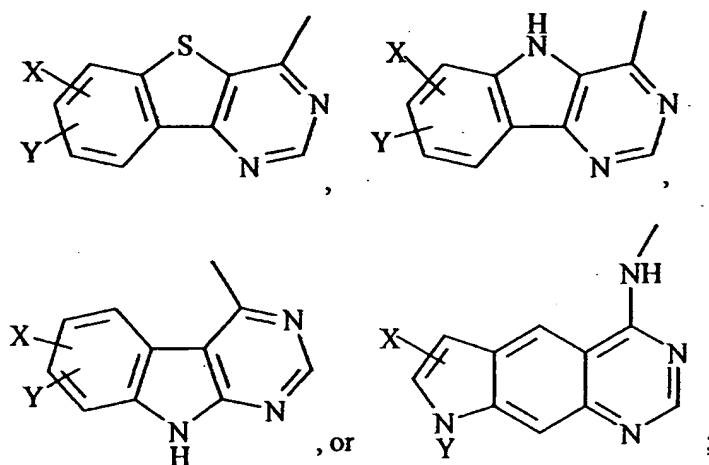
25 In another embodiment, the present invention provides compounds having  
 the Formula II

Q-Z

II

wherein Q is

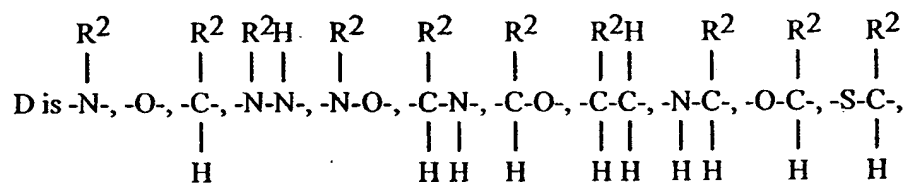
-50-



$p$  is 0 or 1;

X is -D-E-F, and Y is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, or X is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, and Y is -D-E-F;

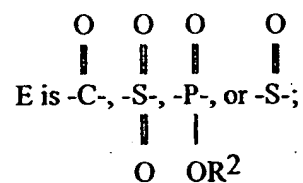
5



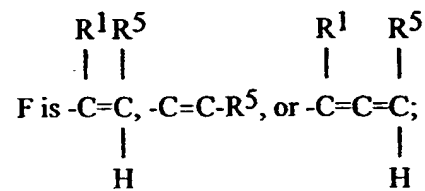
10

or absent;

15



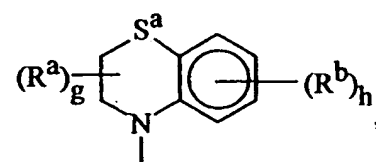
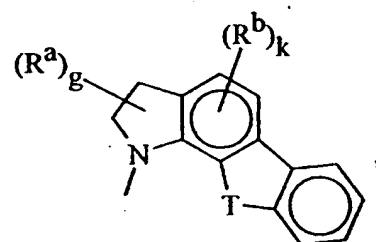
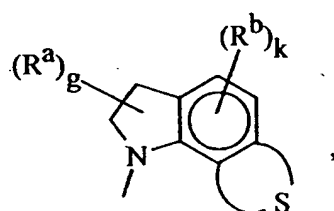
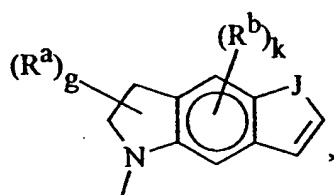
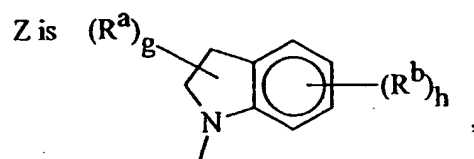
20



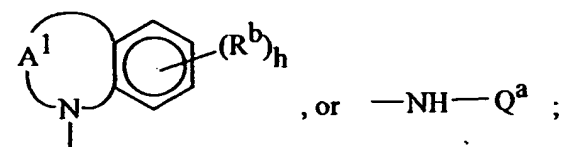
-51-

provided that when E is -S- or -S-, D is not -N-C-, or -OC-;

5



10



-52-

- each R<sup>a</sup> is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)  
alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not  
attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R<sup>a</sup> is  
independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)  
5 alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-  
(C<sub>1</sub>-C<sub>4</sub>)alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl,  
(C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl, or (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- each R<sup>b</sup> is independently mono-, di-, or trifluoromethyl, halo, nitro, hydroxy,  
10 amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy,  
benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl,  
(C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino,  
trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl,  
N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino,  
15 trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or  
(C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said  
phenyl, benzyloxy, phenoxy, and benzoylamino optionally mono-  
substituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and  
said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on  
20 the benzene moiety, or R<sup>b</sup> is -ZaR<sup>77</sup>;
- J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;  
g is 0, 1, or 2;  
h is 0 to 4;  
k is 0, 1, or 2;
- 25 S completes a 5- or 6-membered aromatic or partially saturated ring that can  
contain an oxygen or sulfur atom;  
T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;  
S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the

A  
|

substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are

independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

E<sup>1</sup>, E<sup>2</sup>, or E<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>, hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl,

-54-

C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl,  
 C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto,  
 C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxycarbonyl, C<sub>2</sub>-C<sub>4</sub> alkenyl,  
 C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

5     Z<sup>a</sup> is a bond, -CH<sub>2</sub>-, -S-, SO<sub>2</sub>, -NH-, -O-, -OCH<sub>2</sub>-, -S-CH<sub>2</sub>-, -SO<sub>2</sub>-, or  
       -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>77</sup> is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted  
 heterocyclic aromatic ring;

R<sup>5</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl, 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub>  
 10     alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidiny, -(CH<sub>2</sub>)<sub>n</sub>-piperaziny,   
       -(CH<sub>2</sub>)<sub>n</sub>-piperaziny[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,  
       -(CH<sub>2</sub>)<sub>n</sub>-pyridiny, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazoyl, -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino,  
       -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino, -C=CH<sub>2</sub>, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 15   |  
    H  
       -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine, -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub>alkyl),  
       -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy,  
       (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, phenyl or  
       substituted phenyl, wherein the substituted phenyl can have from one to  
 20     three substituents independently selected from E<sup>1</sup>, E<sup>2</sup>, E<sup>3</sup> or a monocyclic  
       heteroaryl group, and each C<sub>1</sub>-C<sub>6</sub> alkyl group above in R<sup>5</sup> can be  
       substituted with -OH, -NH<sub>2</sub> or -NAB, where A and B are as defined above  
       or C<sub>1</sub>-C<sub>6</sub> alkyl; and

25     n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs  
       thereof.

The term "alkyl" means a straight or branched chain hydrocarbon.  
 Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl,  
 isobutyl, butyl, tert-butyl, sec-butyl, pentyl, and hexyl.



The term "alkoxy" means an alkyl group attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy, and isobutoxy.

The term "halogen" includes chlorine, fluorine, bromine, and iodine.

5       The term "alkenyl" means a branched or straight chain hydrocarbon having one or more carbon-carbon double bond.

The term "cycloalkyl" means a cyclic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

10       The term "cycloalkoxy" means a cycloalkyl group attached to an oxygen atom.

The term "perfluoroalkyl" means an alkyl group in which all the hydrogen atoms have been replaced by fluorine atoms.

The term "acyl" means a group derived from an organic acid by removal of the hydroxy group (-OH).

15       The term "acyloxy" means an acyl group attached to an oxygen atom.

The term "thioalkyl" means an alkyl group attached to a sulfur atom.

The term "sulfinylalkyl" means a sulfinyl group attached to an alkyl group.

The term "sulfonylalkyl" means a sulfonyl group attached to an alkyl group.

20       The term "thiocycloalkyl" means a cycloalkyl group attached to a sulfur atom.

The term "sulfinylcycloalkyl" means a sulfinyl group attached to a cycloalkyl group.

25       The term "sulfonylcycloalkyl" means a sulfonyl group attached to a cycloalkyl group.

The term "mercapto" means a -SH group.

The term "alkoxycarbonyl" means an alkoxy group attached to a carbonyl group.

30       The term "cycloalkoxycarbonyl" means a cycloalkoxy group attached to a carbonyl group.

The term "cycloalkenyl" means a cyclic hydrocarbon containing one or more carbon-carbon double bond.

The term "alkynyl" means a hydrocarbon having one or more carbon-carbon triple bond.

The term "monocyclic heteroaryl" mean a heterocyclic aryl compound having only one ring structure. The cyclic compound is aromatic and contains one or more heteroatom. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Examples of monocyclic heteroaryl groups include, but are not limited to, pyridyl, thienyl, and imidazolyl.

The symbol "-" represents a covalent bond.

The compounds of Formulas I or II are irreversible inhibitors of tyrosine kinases, particularly EGF tyrosine kinase. A therapeutically effective amount of the compounds of Formula I or II can be administered to a patient having cancer or a patient having restenosis or at risk of having restenosis or a patient having psoriasis, atherosclerosis, or endometriosis. Those skilled in the art are readily able to identify patients having cancer, restenosis, psoriasis, atherosclerosis, or endometriosis, and patients who are at risk of developing restenosis. The term "patient" means animals such as dogs, cats, cows, sheep, and also includes humans.

The compounds of the present invention can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray. The compounds can be administered alone or as part of a pharmaceutically acceptable composition that includes pharmaceutically acceptable excipients. It is noted that more than one compound of Formula I or II can be administered either concurrently or sequentially.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as

-57-

ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

5        These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought  
10       about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

      Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium  
15       citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid,  
20       certain complex silicates, and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid  
25       polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

      Solid compositions of a similar type may also be employed as fillers in soft- and hard-filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene-glycols, and the like.

30       Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such

composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the  
5 above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers,  
10 as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these  
15 substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending  
20 agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable  
25 non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention  
30 include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic

formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like (see, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J Pharm Sci*, 1977;66:1-19 which is incorporated herein by reference).

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C<sub>1</sub>-C<sub>6</sub> alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C<sub>5</sub>-C<sub>7</sub> cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C<sub>1</sub>-C<sub>4</sub> alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C<sub>1</sub>-C<sub>6</sub> alkyl amines and secondary C<sub>1</sub>-C<sub>6</sub> dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine  
5 may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C<sub>1</sub>-C<sub>3</sub> alkyl primary amines and C<sub>1</sub>-C<sub>2</sub> dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed  
10 in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of  
15 which are incorporated herein by reference.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is sufficient. The  
20 specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

25 The compounds of the present invention can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

In addition, the compounds of the present invention can exist in unsolvated  
30 as well as solvated forms with pharmaceutically acceptable solvents such as water,

-61-

ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

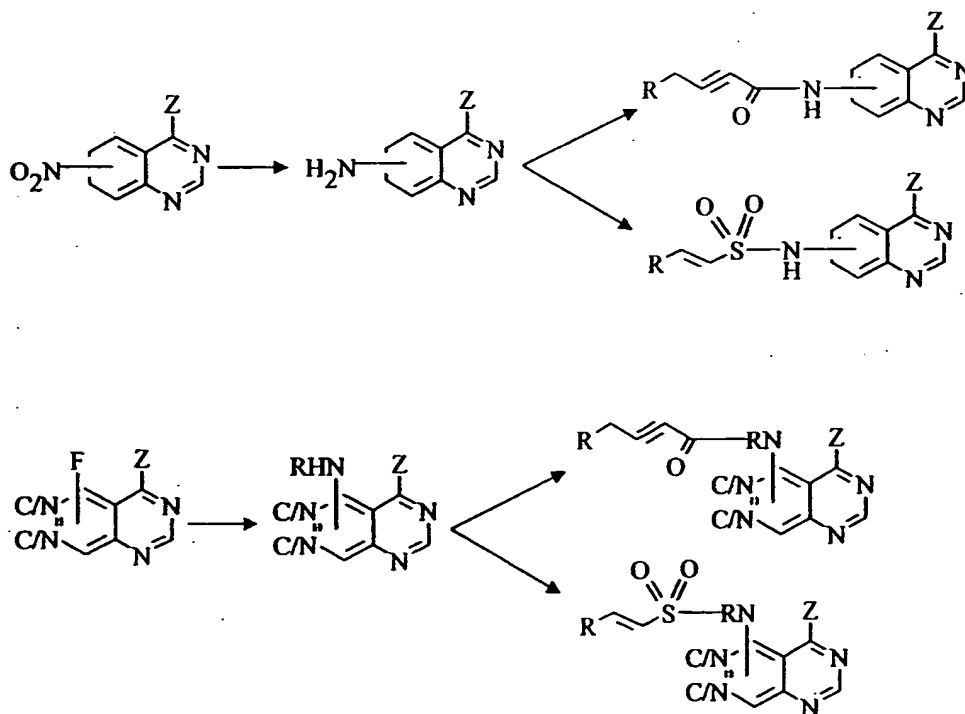
It is intended that the compounds of Formula I, II, or III be either synthetically produced or biologically produced.

- 5           The following examples illustrate particular embodiments of the invention and are not intended to limit the specification, including the claims, in any manner.

### GENERAL SYNTHETIC SCHEMES

#### Amine-Linked Alkylating Michael Acceptor Sidechains

- 10           The amine is acylated either by an acid in the presence of a coupling agent such as EDAC, or by an acid chloride. The amine in turn can be made by reduction of the corresponding nitro compound, displacement of a halogen by an amine or ammonia equivalent, or in the case of pyrido[4,3-d]pyrimidines by direct incorporation during the synthesis. 2-Haloalkylsulfonyl halides form vinyl
- 15           sulfonamides when treated with the aryl amine and excess tertiary amine base.



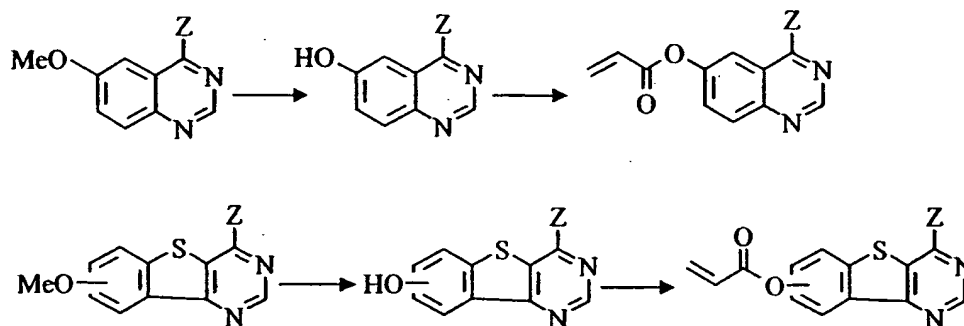
-62-

C/N means either a carbon or nitrogen atom is present at that location.

--- means a bond or no bond.

#### Oxygen-Linked Alkylating Michael Acceptor Sidechains

5 The hydroxyl group is acylated either by an acid in the presence of a coupling agent such as EDAC, or by an acid chloride. The hydroxyl compound can in turn be made by cleavage of the corresponding methyl ether. 3-Methylthioalkanoic acid or their acid chlorides can be used to acylate the oxygen followed by S-alkylation or oxidation and basic or thermal elimination.



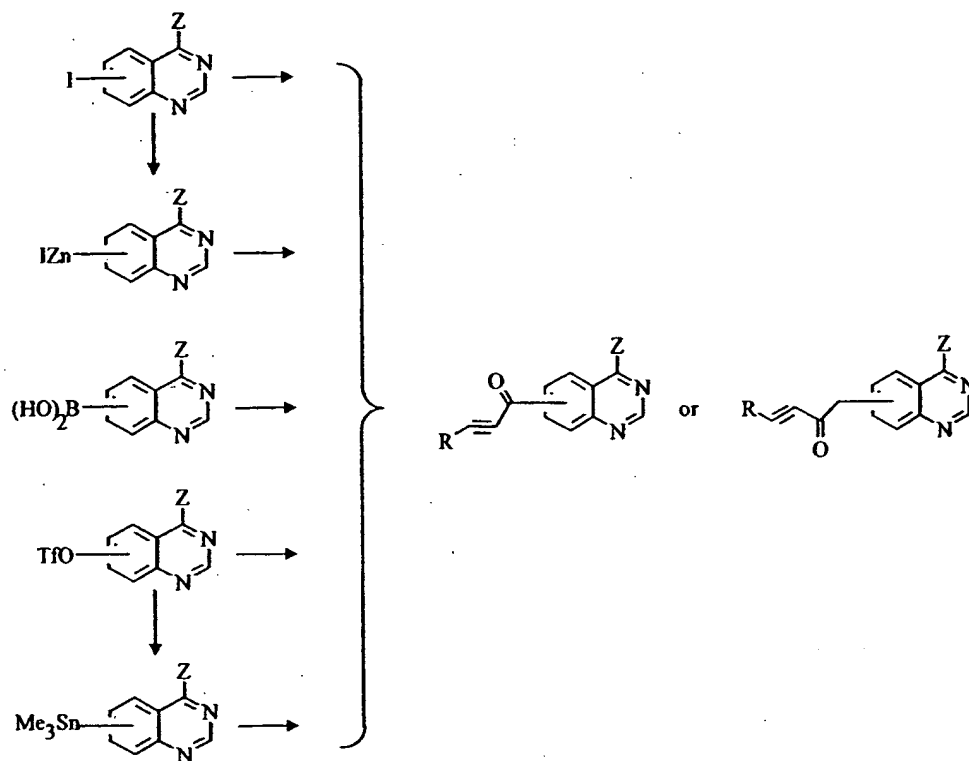
10 Ar and R denote an aryl group and R denotes an organic group as exemplified herein.

#### Carbon-Linked Alkylating Michael Acceptor Sidechains

15 A Stille or Suzuki coupling can be used to couple the sidechain to an appropriately substituted quinazoline/pyridopyrimidine/pyrimidinopyrimidine/tricycle. These in turn can be made as aryl halides by methods known in the art, or as aryl triflates by triflation of the hydroxyl compounds described above, as aryl stannanes by reaction of the abovementioned triflates with hexamethyl distannane, or as arylboronic acids by conversion of aryl iodides to arylorgano-metallics, followed by treatment with borate esters and hydrolysis. Alternatively, aryl iodides  
20 can be converted to the arylzinc species and coupled with activated halides.



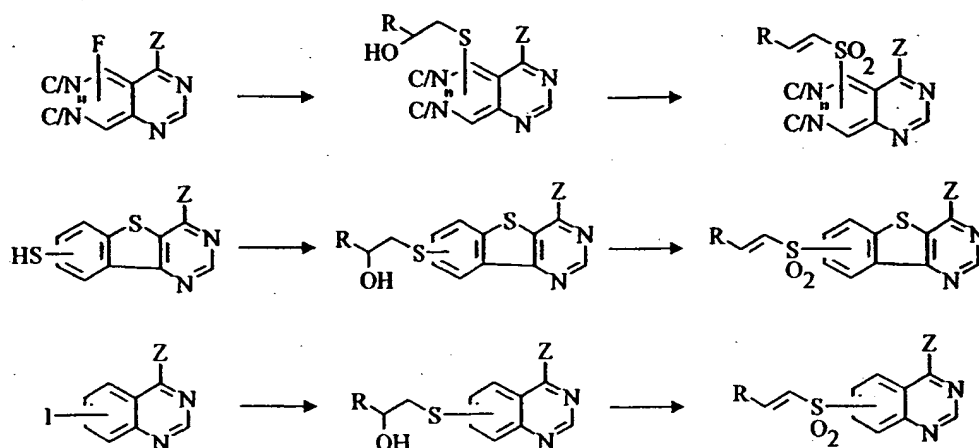
-63-



#### Sulfur-Linked Alkylating Michael Acceptor Sidechains

- Activated halides in pyridopyrimidines and pyrimidinopyrimidines can be displaced by suitable 2-hydroxythiolates, and these in turn can be oxidized to sulfones, and then water eliminated by treatment with mesyl chloride and several equivalents of a base. For quinazolines, and claimed tricycles, either an activated halogen especially fluorine can be used in the sequence just described for pyridopyrimidines, or an aryl iodide precursor can be metalated, quenched with sulfur or a suitable sulfur electrophilic progenitor and then the resultant aryl thiol used to open a terminal epoxide, giving a 2-hydroxy thioether which can be converted onto a vinyl sulfone by oxidation and water elimination as described above.

-64-

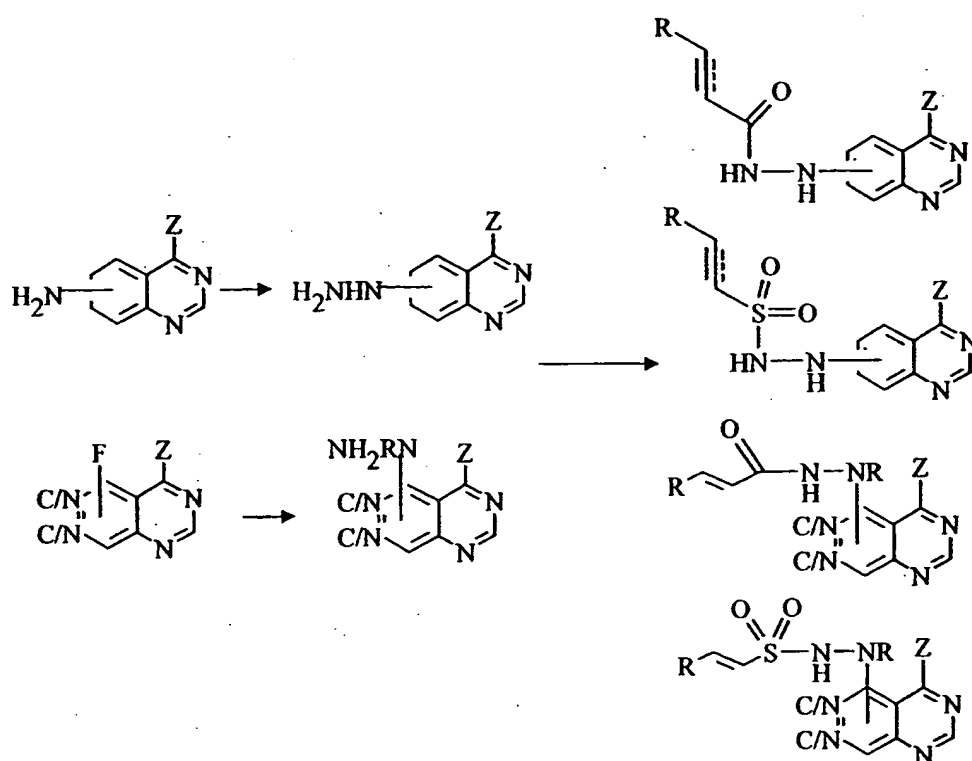


#### Hydrazino-Linked Alkylating Michael Acceptor Sidechains

Activated halides in pyridopyrimidines and pyrimidinopyrimidines and appropriately substituted quinazolines can be displaced by a (N-alkyl) hydrazine.

- 5 Alternatively, an amino-derivative of the desired ring nucleus can be diazotized, and then reduced to the hydrazine. The distal nitrogen of the hydrazine can then be acylated, sulfonylated or phosphorylated, by methods well-known to one skilled in the art.

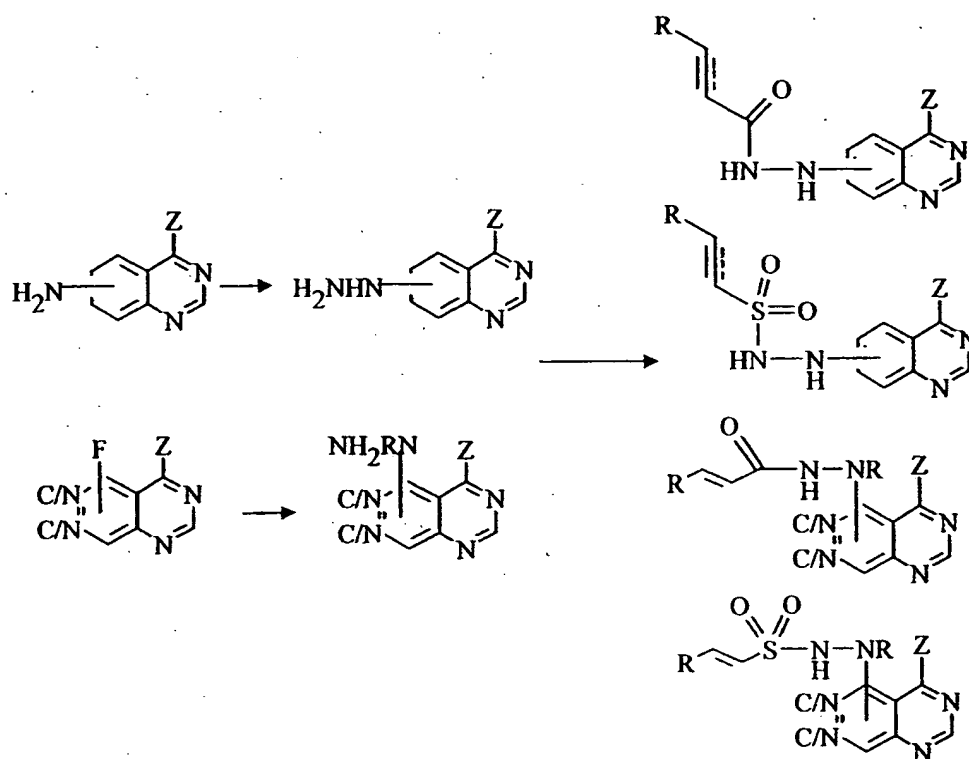
-65-



#### Hydroxylamino-O-Linked Alkylating Michael Acceptor Sidechains

- Activated halides in pyridopyrimidines and pyrimidinopyrimidines and appropriately substituted quinazolines can be displaced by a suitably O-protected (N-alkyl) hydroxylamine. Alternatively, a nitro-derivative of the desired ring nucleus can be synthesized, and then reduced to the hydroxylamine under appropriate mildly reducing conditions. The oxygen of the hydroxylamine can then be acylated, sulfonylated or phosphorylated, by methods well-known to one skilled in the art.

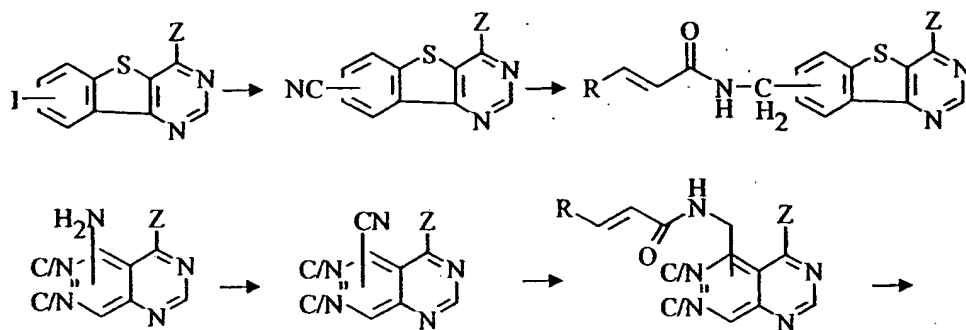
-66-



#### Methyleneamino-N-Linked Alkylating Michael Acceptor Sidechains

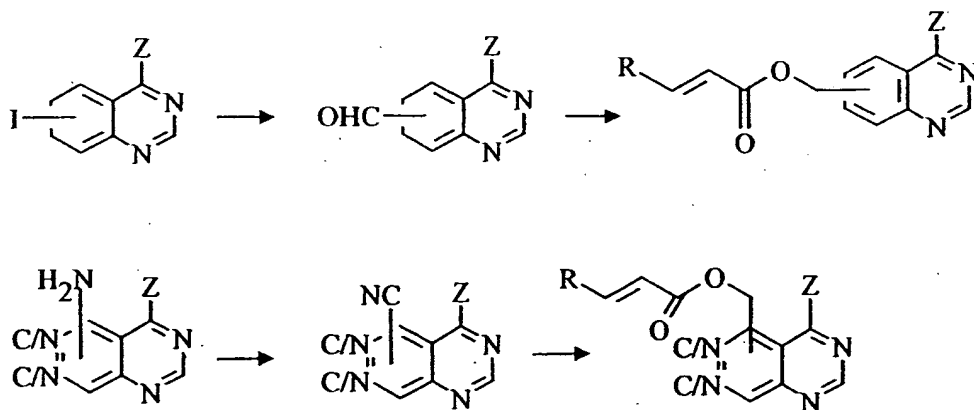
Activated halides in pyridopyrimidines and pyrimidinopyrimidines and appropriately substituted quinazolines can be displaced by cyanide, preferably in the presence of copper or nickel salt catalysis. Alternatively, an amino-derivative of the desired ring nucleus can be diazotized, and then converted to the nitrile as described above. In some cases, the nitrile functionality can be incorporated into the heterocycle earlier in the synthesis, either as itself, or via a carboxylic acid or aldehyde, both of which can readily be turned into nitrile compounds by one skilled in the art. Reduction of the nitrile to a methyleneamine is followed by nitrogen acylation, sulfonylation or phosphorylation, by methods well-known to one skilled in the art.

-67-



#### Methyleneoxy-O-Linked Alkylating Michael Acceptor Sidechains

Hydroxymethyl compounds can be incorporated into appropriate heterocycles in many ways obvious to one skilled in the art. For example, iodoquinazolines may be carbonylated in a Heck reaction, and then reduced with NaBH<sub>4</sub> to the desired precursor. Aminopyridopyrimidines may be diazotized, converted to the nitrile, partially reduced to an imine, hydrolysed, and the resultant aldehyde reduced to hydroxymethyl. The oxygen of the hydroxymethyl can then be acylated, sulfonylated or phosphorylated, by methods well-known to one skilled in the art.

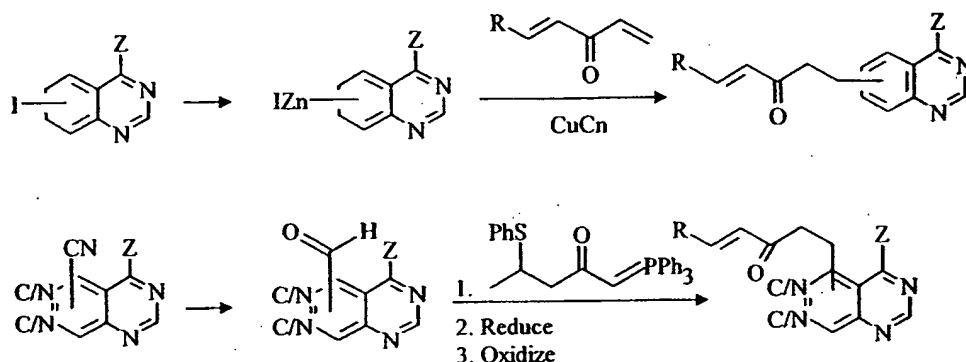


#### Ethano-Linked Alkylating Michael Acceptor Sidechains

Michael addition of a cuprate, derived via an organozincate from an iodoquinazoline, to a divinylketone, or appropriately mono-masked derivative, followed by unmasking of the second unsaturated functionality, if required, will give compounds of the desired type. Aldehydes derived from pyridopyrimidines or

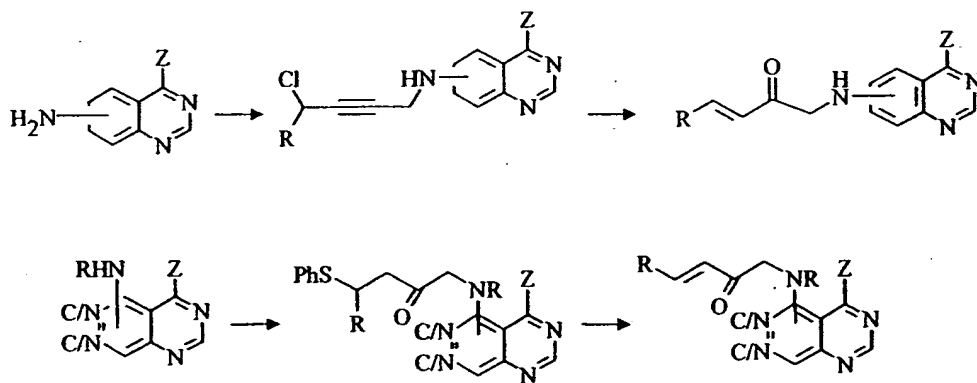
-68-

pyrimidopyrimidines as described above can be homologated to the desired compounds by a wide variety of techniques such as the one illustrated, by one skilled in the art.



#### 5 Aminomethyl-C-Linked Alkylating Michael Acceptor Sidechains

Amino-heterocycles of the type described throughout this application can be alkylated by various double bond-masked equivalents of 1-bromobut-3-en-2-one, followed by unmasking of the unsaturation by methods known to one skilled in the art.



10

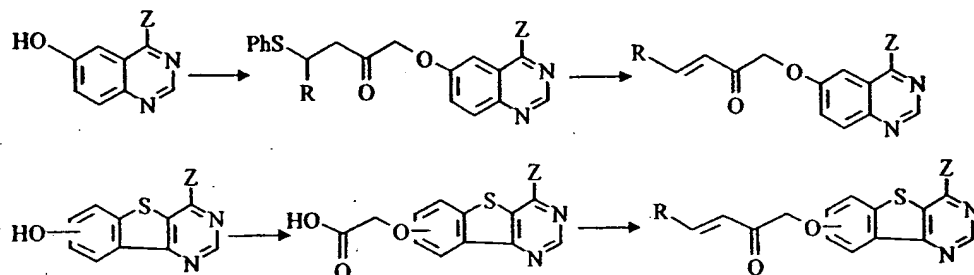
#### Hydroxymethyl-C-Linked Alkylating Michael Acceptor Sidechains

Hydroxy-heterocycles made as described previously from methoxy-heterocycles can be alkylated by various double bond-masked equivalents of 1-bromobut-3-en-2-one, followed by unmasking of the unsaturation by methods known to one skilled in the art. Alternatively, alkylation of the phenol can be

15

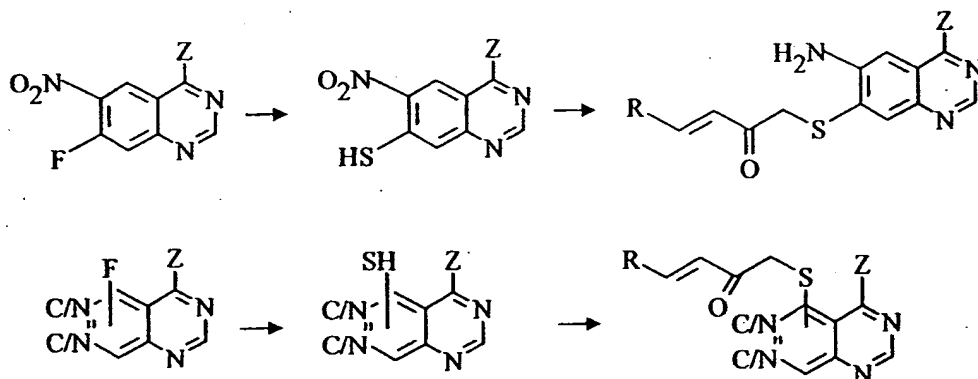
-69-

accomplished with chloroacetic acid, followed by conversion to an acyl chloride and Stille coupling of that acyl halide with an appropriate alkenyl stannane.



### Thiomethyl-C-Linked Alkylating Michael Acceptor Sidechains

- 5           Appropriate mercapto-heterocycles, made by displacement of activated halides on the heteroaromatic ring, can be alkylated by various double bond-masked equivalents of 1-bromobut-3-en-2-one, followed by unmasking of the unsaturation by methods known to one skilled in the art. Alternatively, alkylation of the thiol can be accomplished with chloroacetic acid, followed by conversion to an acyl chloride and Stille coupling of that acyl halide with an appropriate alkenyl stannane.
- 10



### EXAMPLE 1

**N-[4-(6-Bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide**

- 15   **Step (a) 6-Nitro-4-(1-(6-bromo-indolinyl))-quinazoline**

A suspension of 6-bromo-indoline (490 mg, 2.47 mmol) (Miyake Y., Kikugawa Y., *J. Het. Chem.*, 1983;20:349), 4-chloro-6-nitro-quinazoline (660 mg,

-70-

2.47 mmol), and N,N-dimethylaniline (0.63 mL, 4.9 mmol) in 15 mL of isopropyl alcohol was heated under reflux for 1 hour. The suspension was concentrated to give a solid, which was shaken with a mixture of ethyl acetate and saturated aqueous sodium bicarbonate. The solid was collected by filtration and  
5 recrystallized from a boiling mixture of ethanol (100 mL) and dimethylformamide (25 mL) to give the product as a yellow solid (290 mg, 32%), mp 249-251°C.

Anal. Calcd. for  $C_{16}H_{11}BrN_4O_2$ :

C, 51.77; H, 2.99; N, 15.09.

Found: C, 51.58; H, 2.91; N, 15.01.

10 MS (APCI): Calcd. for  $M + 1$ , 371.0; Found, 371.0

**Step (b) 6-Amino-4-(1-(6-bromo-indoliny))-quinazoline**

To a suspension of 6-nitro-4-(1-(6-bromo-indoliny))-quinazoline (240 mg, 6.5 mmol) and acetic acid (1.04 mL, 18 mmol) in  $H_2O$  (75 mL) and ethanol (100 mL), heated under reflux, was added iron powder (washed with 1N HCl, then  
15  $H_2O$ , and dried; 180 mg, 3.23 mmol). After 30 minutes of heating, more iron powder (320 mg, 5.73 mmol) was added, and heating was continued for another 30 minutes. The reaction was filtered while hot and the solids washed with ethanol. To the filtrate and washings was added concentrated  $NH_4OH$  (10 mL), and a small amount of solid was removed by filtration. The filtrate was  
20 concentrated, and the resulting residue was purified by flash silica gel chromatography dichloromethane/methanol, 10:1) to give a yellow foam.  
MS (APCI): Calcd. for  $C_{16}H_{13}BrN_4$ :  $M + 1$ , 341.0; Found, 341.1

The NMR spectrum showed the presence of an acetate species. This was removed by dissolving the solid in diethylether, and washing the solution  
25 consecutively with  $H_2O$ , saturated aqueous  $NaHCO_3$ , and brine. The solution was dried ( $MgSO_4$ ) and concentrated to give the product as a brown solid (220 mg, 100%).



-71-

**Step (c)**

To a suspension of 6-amino-4-(1-(6-bromo-indoliny))-quinazoline (200 mg, 0.6 mmol) and N-ethyl-N'-(3-N,N-dimethylaminopropylcarbodiimide hydrochloride) (450 mg, 2.3 mmol) in dimethylformamide (1 mL) and tetrahydrofuran (3 mL), cooled in an ice-bath and under nitrogen, was added acrylic acid (0.16 mL, 2.3 mmol), followed by diisopropylethylamine (0.40 mL, 2.3 mmol). The ice-bath was removed, and the suspension was stirred at room temperature for 18 hours. The resulting solution was poured into cold H<sub>2</sub>O, and the suspension was extracted with dichloromethane (4 × 25 mL). The extracts were dried (MgSO<sub>4</sub>), concentrated, and purified by flash silica gel chromatography (dichloromethane/methanol, 9:1) to give the product as a light yellow solid (110 mg, 41%), mp 214-216°C. This material contained 0.3 mol of dimethylformamide (substantiated by NMR) and 0.3 mol H<sub>2</sub>O by C,H,N analysis. Anal. Calcd. for C<sub>19</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>1</sub>·0.3DMF·0.3H<sub>2</sub>O:

C, 56.56; H, 4.22; N, 14.25.

Found: C, 56.37; H, 4.14; N, 14.01.

MS (APCI): Calcd. for M + 1, 395.0; Found, 395.1

**BIOLOGICAL METHODS**Tissue Culture

A431 human epidermoid carcinoma cells were obtained from the American Type Culture Collection, Rockville, MD and maintained as monolayers in dMEM (Dulbecco's modified eagle medium)/F12, 50:50 (Gibco/BRL) containing 10% fetal bovine serum. For growth inhibition assays, dilutions of the designated compound in 10 µL were placed in 24-well Linbro plates (1.7 × 1.6 cm, flat bottom) followed by the addition of cells (2 × 10<sup>4</sup>) in 2 mL of media. The plates were incubated for 72 hours at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub> in air. Cell growth was determined by cell count with a Coulter Model AM electronic cell counter (Coulter Electronics, Inc., Hialeah, FL).

-72-

Purification of Epidermal Growth Factor Receptor Tyrosine Kinase

Human EGF receptor tyrosine kinase was isolated from A431 human epidermoid carcinoma cells by the following method. Cells were grown in roller bottles in dMEM/F12 media (Gibco/BRL) containing 10% fetal calf serum.

- 5 Approximately  $10^9$  cells were lysed in 2 volumes of buffer containing 20 mM N-[2-hydroxyethyl]piperazine-N'-[2-ethane sulfonic acid](Hepes), pH 7.4, 5 mM ethylene glycol-bis( $\beta$ -aminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1% Triton X-100, 10% glycerol, 0.1 mM sodium orthovanadate, 5 mM sodium fluoride, 4 mM pyrophosphate, 4 mM benzamide, 1 mM dithiothreitol (DTT),  
10 80  $\mu$ g/mL aprotinin, 40  $\mu$ g/mL leupeptin, and 1 mM phenylmethyl sulfonyl fluoride (PMSF). After centrifugation at  $25,000 \times g$  for 10 minutes, the supernatant was applied to a fast Q sepharose column (Pharmacia Biotech., Inc., Piscataway, NJ) and eluted with a linear gradient from 0.1 M NaCl to 0.4 M NaCl in 50 mM Hepes, 10% glycerol, pH 7.4. Enzyme active fractions were pooled,  
15 divided into aliquots, and stored at  $-100^\circ\text{C}$ . Fibroblast growth factor receptor (FGFR), platelet-derived growth factor (PDGF), insulin, and c-src tyrosine kinases were obtained by methods well-known in the art. For example, see Fry et al., "Strategies For The Discovery Of Novel Tyrosine Kinase Inhibitors With Anticancer Activity, *Anticancer Drug Design*, 1994;9:331-351.

20 Tyrosine Kinase Assays

- Enzyme assays for  $\text{IC}_{50}$  determinations were performed in 96-well filter plates (Millipore MADVN6550, Millipore, Bedford, MA). The total volume was 0.1 mL containing 20 mM Hepes, pH 7.4, 50  $\mu$ M sodium vanadate, 40 mM magnesium chloride, 10  $\mu$ M adenosine triphosphate (ATP) containing 0.5  $\mu$ Ci of  
25 [ $^{32}\text{P}$ ]ATP, 20  $\mu$ g of poly Glutamic acid/tyrosine (Sigma Chemical Co., St. Louis, MO), 10 ng of EGF receptor tyrosine kinase and appropriate dilutions of inhibitor. All components except the ATP are added to the well and the plate incubated with shaking for 10 minutes at  $25^\circ\text{C}$ . The reaction is started by adding [ $^{32}\text{P}$ ]ATP, and the plate is incubated at  $25^\circ\text{C}$  for 10 minutes. The reaction is terminated by

-73-

addition of 0.1 mL of 20% trichloroacetic acid (TCA). The plate is kept at 4°C for at least 15 minutes to allow the substrate to precipitate. The wells are then washed 5 times with 0.2 mL of 10% TCA and <sup>32</sup>P incorporation determined with a Wallac beta plate counter (Wallac, Inc., Gaithersburg, PA). Assays using intracellular kinase domains of PDGF, FGF, and insulin receptors, as well as those for c-src, were performed as described for the EGF receptor except that 10 mM Manganese chloride was included in the reaction.

#### Western Blotting Procedure

Extracts were made by lysing the monolayers in 0.2 mL of boiling Laemlli buffer (2% sodium dodecyl sulfate, 5% beta-mercaptoethanol, 10% glycerol and 50 mM tris[hydroxymethyl]aminomethane (Tris), pH 6.8), and the lysates were heated to 100°C for 5 minutes. Proteins in the lysate were separated by polyacrylamide gel electrophoresis and electrophoretically transferred to nitrocellulose. The membrane was washed once in 10 mM Tris, pH 7.2, 150 mM NaCl, 0.01% Azide (TNA), and blocked overnight in TNA containing 5% bovine serum albumin and 1% ovalbumin. The membrane was blotted for 2 hours with antiphosphotyrosine antibody (UBI, 1 µg/mL in blocking buffer) and then washed twice in TNA, once in TNA containing 0.05% Tween-20 detergent and 0.05% nonidet P-40 detergent and twice in TNA. The membranes were then incubated for 2 hours in blocking buffer containing 0.1 µCi/mL of [<sup>125</sup>I]protein A and then washed again as above. After the blots were dry, they were loaded into a film cassette and exposed to X-AR X-ray film (Eastman Kodak Co., Rochester, NY) for 1 to 7 days. Band intensities were determined with a Molecular Dynamics laser densitometer.

#### Autophosphorylation Assay

A431 human epidermoid carcinoma cells were grown in 6-well plates to about 80% confluency and then incubated in serum-free media for 18 hours. Duplicate sets of cells were treated with a range of concentrations of the designated compound to be tested as an inhibitor for 15 minutes. The cells were

-74-

then stimulated with 100 ng/mL of EGF for 5 minutes and extracts made as described under the Western Blotting Procedure.

#### Irreversibility Test Protocol

5 A431 human epidermoid carcinoma cells were grown in 6-well plates to about 80% confluency and then incubated in serum-free media for 18 hours. Duplicate sets of cells were treated with 2  $\mu$ M of designated compound to be tested as an irreversible inhibitor for either 1 or 2 hours. One set of cells was then stimulated with 100 ng/mL of EGF for 5 minutes and extracts made as described under the western blotting procedure. The other set of cells were washed free of  
10 the compound with warmed serum-free media, incubated for 2 hours, washed again, incubated another 2 hours, washed again, and then incubated a further 4 hours. This set of cells was then stimulated with EGF and extracts made similar to the first set of cells.

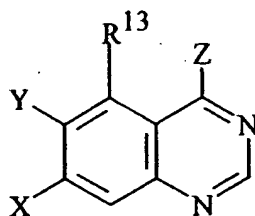
Example Number	IC <sub>50</sub> (nM) EGFr (isolated enzyme assay)	IC <sub>50</sub> (nM) A431 Cell Autophosphorylation Assay	Irreversibility Test
1	0.4	9.9	yes, irreversible

-75-

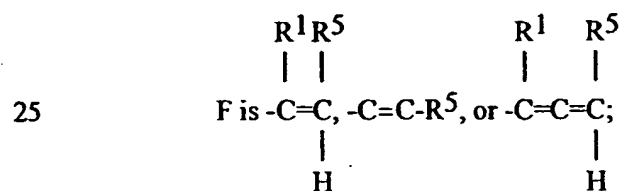
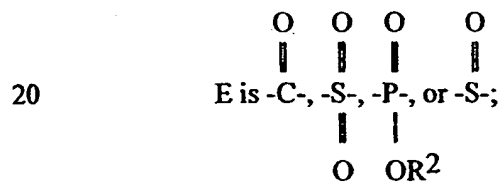
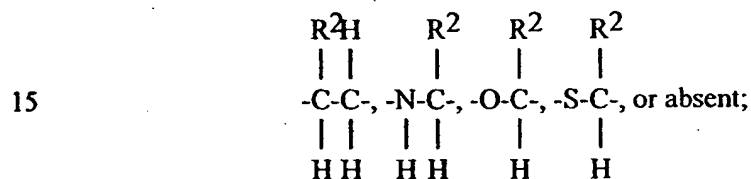
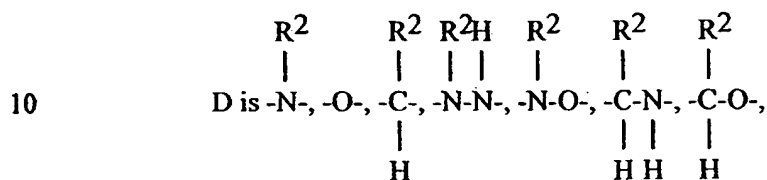
## CLAIMS

What is claimed is:

1. A compound having the Formula I



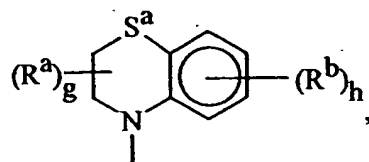
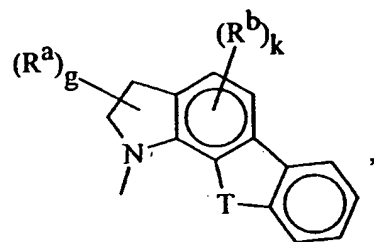
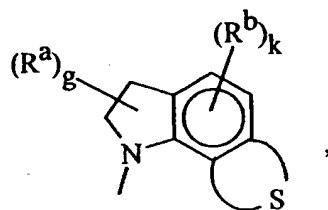
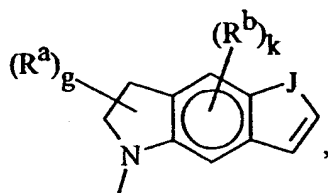
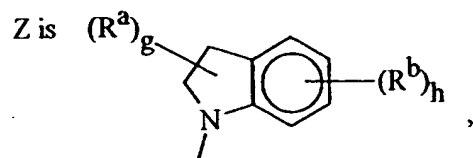
- 5 wherein X is -D-E-F and Y is -SR<sup>4</sup>, halogen, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen,  
or X is -SR<sup>4</sup>, halogen, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, and Y is  
-D-E-F;



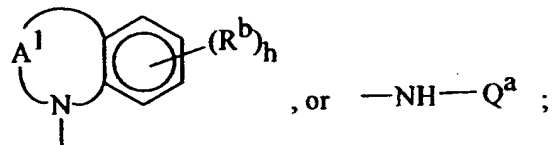
-76-

provided that when E is -S- or -S-, D is not  $\begin{array}{c} \text{O} \quad \text{O} \\ | \quad | \\ \text{N}-\text{C} \\ | \quad | \\ \text{H} \quad \text{H} \end{array}$ , or  $\begin{array}{c} \text{R}^2 \\ | \\ \text{OC} \\ | \\ \text{H} \end{array}$ ;

5



10



-77-

each R<sup>a</sup> is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)

alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or -N-), or R<sup>a</sup> is independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>) alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or di-N,N-(C<sub>1</sub>-C<sub>4</sub>) alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl, morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl, 4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl, sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>b</sup> is independently mono-, di-, or trifluoromethyl, halo, nitro,

hydroxy, amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino, trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally monosubstituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R<sup>b</sup> is -Z<sup>a</sup>R<sup>77</sup>;

J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;

-78-

T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;

S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein

A  
|

the substituents are selected from -OH, NH<sub>2</sub>, or -N-B, A and B are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;



-79-

$Z^1$ ,  $Z^2$ , or  $Z^3$  are independently hydrogen, halogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_8$  cycloalkyl,  $C_1$ - $C_6$  alkoxy,  $C_3$ - $C_8$  cycloalkoxy, nitro,  $C_1$ - $C_6$  perfluoroalkyl, hydroxy,  $C_1$ - $C_6$  acyloxy,  $-NH_2$ ,  $-NH(C_1-C_6 \text{ alkyl})$ ,  $-N(C_1-C_6 \text{ alkyl})_2$ ,  $-NH(C_3-C_8 \text{ cycloalkyl})$ ,  $-N(C_3-C_8 \text{ cycloalkyl})_2$ , hydroxymethyl,  $C_1$ - $C_6$  acyl, cyano, azido,  $C_1$ - $C_6$  thioalkyl,  $C_1$ - $C_6$  sulfinylalkyl,  $C_1$ - $C_6$  sulfonylalkyl,  $C_3$ - $C_8$  thiocycloalkyl,  $C_3$ - $C_8$  sulfinylcycloalkyl,  $C_3$ - $C_8$  sulfonylcycloalkyl, mercapto,  $C_1$ - $C_6$  alkoxycarbonyl,  $C_3$ - $C_8$  cycloalkoxycarbonyl,  $C_2$ - $C_4$  alkenyl,  $C_4$ - $C_8$  cycloalkenyl, or  $C_2$ - $C_4$  alkynyl;

$Z^a$  is a bond,  $-CH_2-$ ,  $-S-$ ,  $SO_2$ ,  $-NH-$ ,  $-O-$ ,  $-OCH_2-$ ,  $-S-CH_2-$ ,  $-SO_2-$ , or  $-CH_2CH_2-$ ;

$R^{77}$  is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

$R^5$  is hydrogen, halogen,  $C_1$ - $C_6$  perfluoroalkyl, 1,1-difluoro( $C_1$ - $C_6$ )alkyl,  $C_1$ - $C_6$  alkyl,  $-(CH_2)_n$ -N-piperidiny,  $-(CH_2)_n$ -piperaziny,  $-(CH_2)_n$ -piperaziny[ $N_4$ -( $C_1$ - $C_6$ )alkyl],  $-(CH_2)_n$ -N-pyrrolidyl,  $-(CH_2)_n$ -pyridiny,  $-(CH_2)_n$ -N-imidazoyl,  $-(CH_2)_n$ -N-morpholino,  $-(CH_2)_n$ -N-thiomorpholino,  $-C=CH_2$ ,  $-CH=CH-(C_1-C_6)$ alkyl,

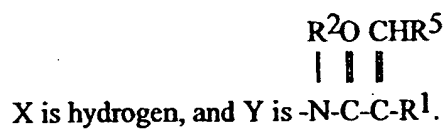
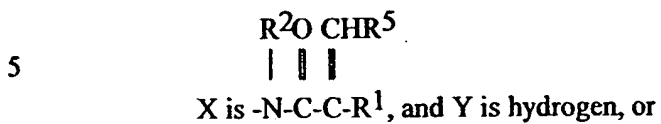
|  
H

$-(CH_2)_n$ -N-hexahydroazepine,  $-(CH_2)_nNH_2$ ,  $-(CH_2)_nNH$  ( $C_1$ - $C_6$ alkyl),  $-(CH_2)_nN(C_1-C_6$ alkyl) $_2$ , -1-oxo( $C_1$ - $C_6$ )alkyl, carboxy, ( $C_1$ - $C_6$ )alkyloxycarbonyl, N-( $C_1$ - $C_6$ )alkylcarbamoyl, phenyl or substituted phenyl, wherein the substituted phenyl can have from one to three substituents independently selected from  $Z^1$ ,  $Z^2$ ,  $Z^3$  or a monocyclic heteroaryl group, and each  $C_1$ - $C_6$  alkyl group can be substituted with  $-OH$ ,  $-NH_2$  or  $-NAB$ , where A and B are as defined above; and

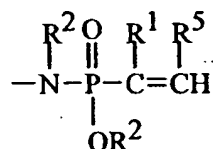
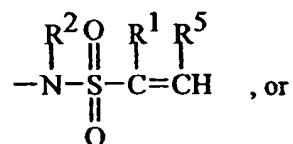
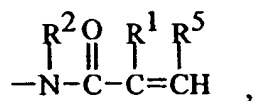
-80-

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

2. A compound of Claim 1 wherein

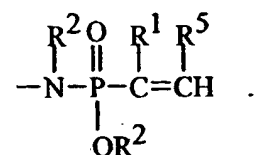
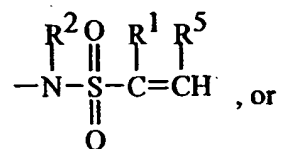
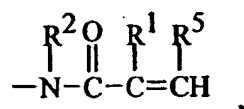


- 10 3. A compound of Claim 1 wherein Y is -D-E-F and -D-E-F is



4. A compound of Claim 1 wherein X is -D-E-F and -D-E-F is

-81-



5. A compound of Claim 3 wherein  $\text{R}^2$  is hydrogen.
6. A compound of Claim 4 wherein  $\text{R}^2$  is hydrogen.
7. A compound of Claim 3 wherein  $\text{R}^2$  is  $-(\text{CH}_2)_n$ -morpholino.
- 5 8. A compound of Claim 4 wherein  $\text{R}^2$  is  $-(\text{CH}_2)_n$ -morpholino.
9. A compound of Claim 3 wherein  $\text{R}^5$  is carboxy,  $(\text{C}_1\text{-C}_6)$ alkyloxycarbonyl or  $\text{C}_1\text{-C}_6$  alkyl.
10. A compound of Claim 1 wherein Y is -D-E-F, and X is  $-\text{O}-(\text{CH}_2)_n$ -morpholino.
- 10 11. A compound of Claim 1 wherein Y is -D-E-F, and X is  $-\text{O}-(\text{CH}_2)_n\text{-N}_1$ -piperazinyl $[\text{N}_4\text{-(C}_1\text{-C}_6\text{)alkyl}]$ .
12. A compound of Claim 1 wherein Y is -D-E-F and X is  $-\text{O}-(\text{CH}_2)_n$ -imidazolyl.

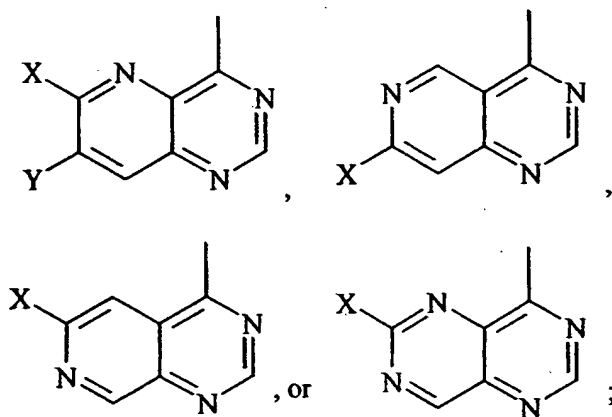
-82-

13. A compound having the Formula II

Q-Z

II

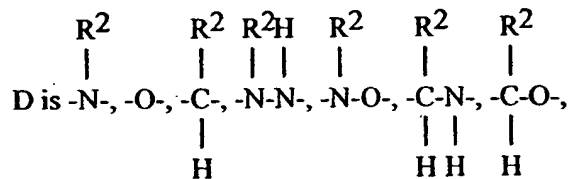
wherein Q is



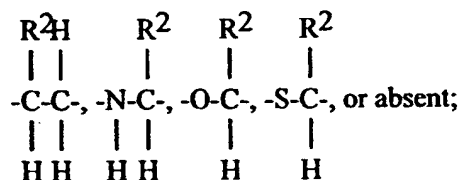
5

X is -D-E-F and Y is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, or X is -SR<sup>4</sup>,-OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, and Y is -D-E-F;

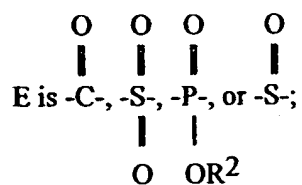
10



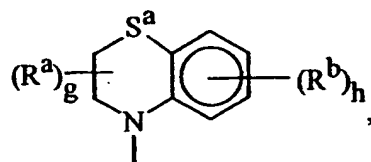
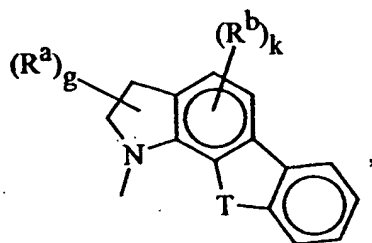
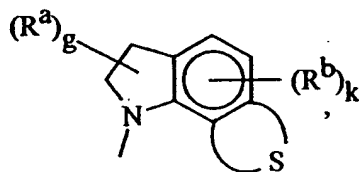
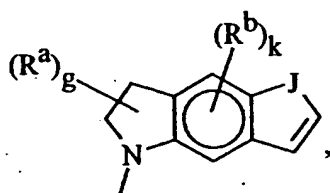
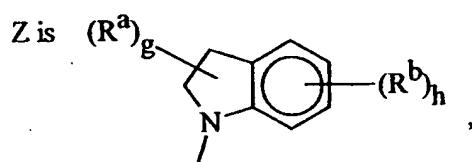
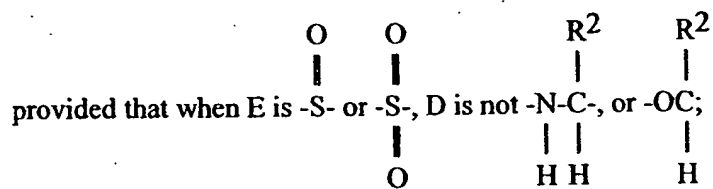
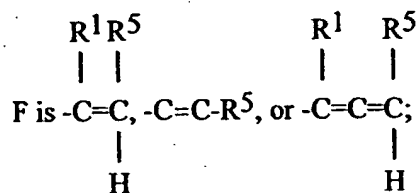
15



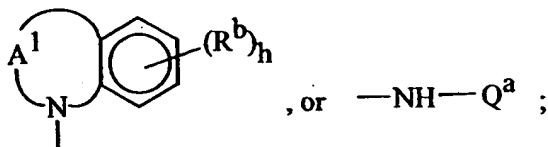
20



-83-



-84-



each R<sup>a</sup> is independently hydroxy, amino, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)

alkylamino, sulfo, or (C<sub>1</sub>-C<sub>4</sub>)alkoxy (provided that such groups are not attached to a ring carbon which is adjacent to an oxy, thio, or

-N-), or R<sup>a</sup> is independently carboxy, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl,

(C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>) alkyl, amino(C<sub>1</sub>-C<sub>4</sub>)alkyl, mono-N- or

di-N,N-(C<sub>1</sub>-C<sub>4</sub>) alkylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl,

morpholino(C<sub>1</sub>-C<sub>4</sub>)alkyl, 4-(C<sub>1</sub>-C<sub>4</sub>)alkyl-piperazin-1-

yl(C<sub>1</sub>-C<sub>4</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxycarbonyl,

sulfo(C<sub>1</sub>-C<sub>4</sub>)alkyl or (C<sub>1</sub>-C<sub>4</sub>)alkyl;

each R<sup>b</sup> is independently mono-, di-, or trifluoromethyl, halo, nitro,

hydroxy, amino, axido, isothiocyano, (C<sub>1</sub>-C<sub>4</sub>)alkyl, phenyl, thienyl,

(C<sub>1</sub>-C<sub>4</sub>)alkoxy, benzyloxy, phenoxy, (C<sub>2</sub>-C<sub>6</sub>)alkenyl,

(C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino,

trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino,

(C<sub>1</sub>-C<sub>4</sub>)alkanoyl, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino,

(C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino, trifluoromethylsulfonylamino,

(C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl,

pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl,

benzyloxy, phenoxy, and benzoylamino optionally monosubstituted

with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and said

(C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on

the benzene moiety, or R<sup>b</sup> is -ZaR<sup>77</sup>;

J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;

g is 0, 1, or 2;

-85-

h is 0 to 4;

k is 0, 1, or 2;

S completes a 5- or 6-membered aromatic or partially saturated ring that  
can contain an oxygen or sulfur atom;

5 T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;

S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;

A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;

10 Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated  
derivative thereof, containing one or two nitrogen heteroatoms and  
optionally containing a further heteroatom selected from nitrogen,  
oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl  
moiety, or a hydrogenated derivative thereof, which heterocyclic or  
aryl moiety, or hydrogenated derivatives thereof, may optionally  
15 bear one or two substituents selected from halogen, hydroxy, oxo,  
amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-  
C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and  
(C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,

20 -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,  
-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,  
-(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,  
-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,  
-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein

25

A  
|

the substituents are selected from -OH, NH<sub>2</sub>, or -N-B, A and B are  
independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,  
-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-86-

$-(CH_2)_n-N_1$ -piperazinyl [ $N_4-(C_1-C_6)$ alkyl],  $-(CH_2)_n-N$ -pyrrolidyl,

$-(CH_2)_n-N$ -pyridyl,  $-(CH_2)_n$ -imidazolyl, or  $-(CH_2)_n-N$ -imidazolyl;

$E^1$ ,  $E^2$ , or  $E^3$  are independently hydrogen, halogen,  $C_1-C_6$  alkyl,  $C_3-C_8$  cycloalkyl,  $C_1-C_6$  alkoxy,  $C_3-C_8$  cycloalkoxy, nitro,  $C_1-C_6$  perfluoroalkyl, hydroxy,  $C_1-C_6$  acyloxy,  $-NH_2$ ,  $-NH(C_1-C_6)$  alkyl),  $-N(C_1-C_6)$  alkyl) $_2$ ,  $-NH(C_3-C_8)$  cycloalkyl),  $-N(C_3-C_8)$  cycloalkyl) $_2$ , hydroxymethyl,  $C_1-C_6$  acyl, cyano, azido,  $C_1-C_6$  thioalkyl,  $C_1-C_6$  sulfinylalkyl,  $C_1-C_6$  sulfonylalkyl,  $C_3-C_8$  thiocycloalkyl,  $C_3-C_8$  sulfinylcycloalkyl,  $C_3-C_8$  sulfonylcycloalkyl, mercapto,  $C_1-C_6$  alkoxycarbonyl,  $C_3-C_8$  cycloalkoxycarbonyl,  $C_2-C_4$  alkenyl,  $C_4-C_8$  cycloalkenyl, or  $C_2-C_4$  alkynyl;

$Z^a$  is a bond,  $-CH_2-$ ,  $-S-$ ,  $SO_2$ ,  $-NH-$ ,  $-O-$ ,  $-OCH_2-$ ,  $-S-CH_2-$ ,  $-SO_2-$ , or  $-CH_2CH_2-$ ;

$R^{77}$  is phenyl, substituted phenyl, or a 5- to 10-membered optionally substituted heterocyclic aromatic ring;

$R^5$  is hydrogen, halogen,  $C_1-C_6$  perfluoroalkyl, 1,1-difluoro( $C_1-C_6$ )alkyl,

$C_1-C_6$  alkyl,  $-(CH_2)_n-N$ -piperidiny,  $-(CH_2)_n$ -piperazinyl,

$-(CH_2)_n$ -piperazinyl [ $N_4-(C_1-C_6)$ alkyl],  $-(CH_2)_n-N$ -pyrrolidyl,

$-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n-N$ -imidazolyl,  $-(CH_2)_n-N$ -morpholino,

$-(CH_2)_n-N$ -thiomorpholino,  $-C=CH_2$ ,  $-CH=CH-(C_1-C_6)$ alkyl,

|  
H

$-(CH_2)_n-N$ -hexahydroazepine,  $-(CH_2)_nNH_2$ ,  $-(CH_2)_nNH$

$(C_1-C_6)$ alkyl),  $-(CH_2)_nN(C_1-C_6)$ alkyl) $_2$ ,  $-1-oxo(C_1-C_6)$ alkyl,

carboxy,  $(C_1-C_6)$ alkyloxycarbonyl,  $N-(C_1-C_6)$ alkylcarbamoyl,

phenyl or substituted phenyl, wherein the substituted phenyl can

have from one to three substituents independently selected from

$E^1$ ,  $E^2$ ,  $E^3$  or a monocyclic heteroaryl group, and each  $C_1-C_6$  alkyl

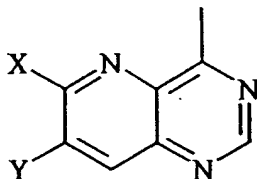


-87-

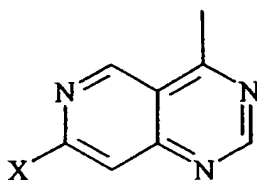
group can be substituted with -OH, -NH<sub>2</sub> or -NAB, where A and B are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

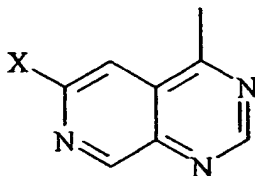
- 5 14. A compound of Claim 13 wherein Q is



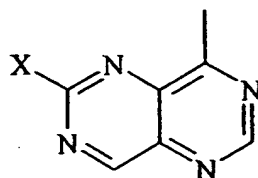
15. A compound of Claim 13 wherein Q is



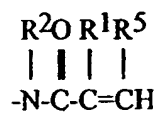
16. A compound of Claim 13 wherein Q is



17. A compound of Claim 13 wherein Q is



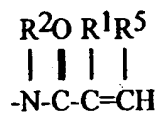
18. A compound of Claim 15 wherein X is



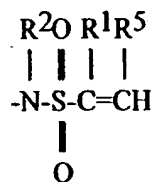
15

-88-

19. A compound of Claim 16 wherein X is

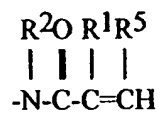


- 5 20. A compound of Claim 16 wherein X is



10

21. A compound of Claim 14 wherein X is



15

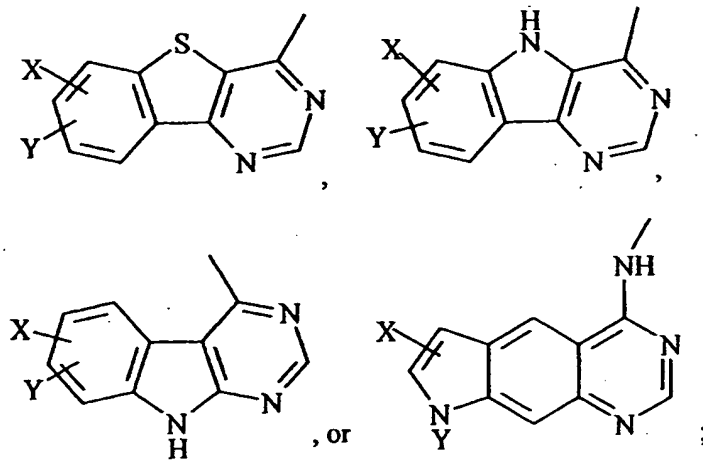
and Y is hydrogen.

22. A compound having the Formula II

Q-Z

II

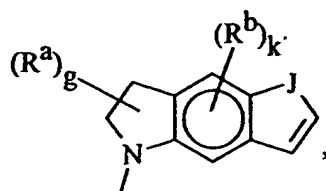
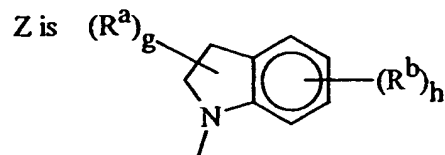
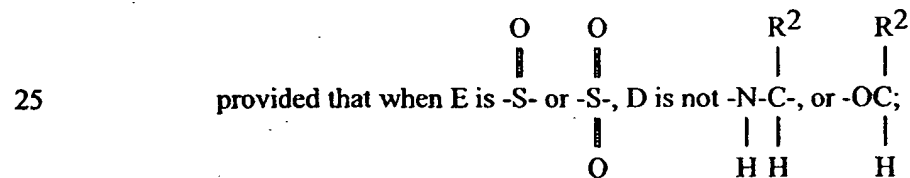
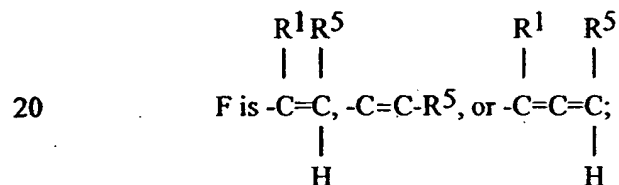
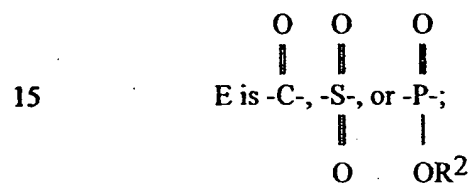
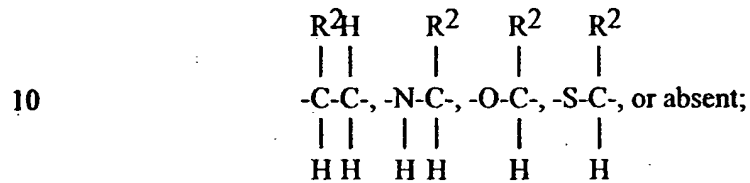
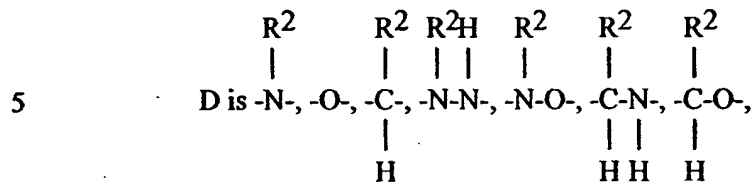
wherein Q is



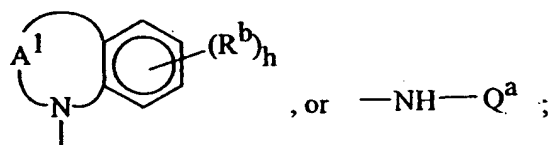
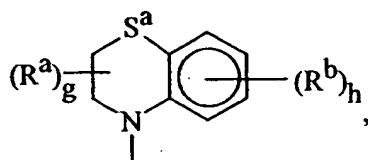
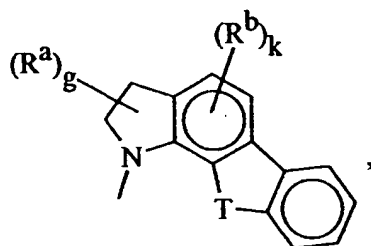
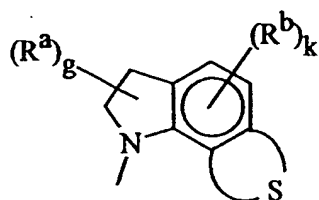
-89-

X is -D-E-F and Y is -SR<sup>4</sup>, -OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, or X is -SR<sup>4</sup>,

-OR<sup>4</sup>, -NHR<sup>3</sup> or hydrogen, and Y is -D-E-F;



-90-



- 5 each  $R^a$  is independently hydroxy, amino, N-mono- or N,N-di-( $C_1$ - $C_4$ )  
alkylamino, sulfo, or ( $C_1$ - $C_4$ )alkoxy (provided that such groups are  
not attached to a ring carbon which is adjacent to an oxy, thio, or  
-N-), or  $R^a$  is independently carboxy, hydroxy( $C_1$ - $C_4$ )alkyl,  
( $C_1$ - $C_4$ )alkoxy( $C_1$ - $C_4$ ) alkyl, amino( $C_1$ - $C_4$ )alkyl, mono-N- or  
10 di-N,N-( $C_1$ - $C_4$ ) alkylamino( $C_1$ - $C_4$ )alkyl,  
morpholino( $C_1$ - $C_4$ )alkyl, 4-( $C_1$ - $C_4$ )alkyl-piperazin-1-  
yl( $C_1$ - $C_4$ )alkyl, carboxy( $C_1$ - $C_4$ )alkyl, ( $C_1$ - $C_4$ )alkoxycarbonyl,  
sulfo( $C_1$ - $C_4$ )alkyl or ( $C_1$ - $C_4$ )alkyl;

- 15 each  $R^b$  is independently mono-, di-, or trifluoromethyl, halo, nitro,  
hydroxy, amino, axido, isothiocyano, ( $C_1$ - $C_4$ )alkyl, phenyl, thienyl,  
( $C_1$ - $C_4$ )alkoxy, benzyloxy, phenoxy, ( $C_2$ - $C_6$ )alkenyl,

-91-

- (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy, cyano, benzoylamino, trifluoromethylcarbonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoylamino, (C<sub>1</sub>-C<sub>4</sub>)alkanoyl, N-mono- or N,N-di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonylamino, trifluoromethylsulfonylamino, (C<sub>1</sub>-C<sub>4</sub>)alkylthio, (C<sub>1</sub>-C<sub>4</sub>)alkylsulfinyl or (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, pyrrol-1-yl, piperidin-1-yl or pyrrolidin-1-yl, said phenyl, benzyloxy, phenoxy, and benzoylamino optionally monosubstituted with halo, nitro, trifluoromethyl, hydroxy, or (C<sub>1</sub>-C<sub>4</sub>)alkyl and said (C<sub>1</sub>-C<sub>4</sub>)alkylenedioxy is linked at both ends to adjacent carbons on the benzene moiety, or R<sup>b</sup> is -Z<sup>a</sup>R<sup>77</sup>;
- J is -CH<sub>2</sub>-, thio, -N(H)-, or oxy;  
g is 0, 1, or 2;  
h is 0 to 4;  
k is 0, 1, or 2;
- S completes a 5- or 6-membered aromatic or partially saturated ring that can contain an oxygen or sulfur atom;  
T is -CH<sub>2</sub>-, -N(H)-, thio, or oxy;  
S<sup>a</sup> is -CH<sub>2</sub>-, oxy, or thio;
- A<sup>1</sup> completes a 7- to 9-membered mono-unsaturated mono-aza ring;
- Q<sup>a</sup> is a 9- or 10-membered bicyclic heterocyclic moiety, or a hydrogenated derivative thereof, containing one or two nitrogen heteroatoms and optionally containing a further heteroatom selected from nitrogen, oxygen and sulfur, or Q<sup>a</sup> is a 9- or 10-membered bicyclic aryl moiety, or a hydrogenated derivative thereof, which heterocyclic or aryl moiety, or hydrogenated derivatives thereof, may optionally bear one or two substituents selected from halogen, hydroxy, oxo, amino, nitro, carbamoyl, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkylamino, di-[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, and (C<sub>2</sub>-C<sub>4</sub>)alkanoylamino;

-92-

R<sup>1</sup> is hydrogen, halogen, or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

5       -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein

A

|

10       the substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are

independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

15       E<sup>1</sup>, E<sup>2</sup>, or E<sup>3</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub>

cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy, nitro, C<sub>1</sub>-C<sub>6</sub>

perfluoroalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> acyloxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub> alkyl),

-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -N(C<sub>3</sub>-C<sub>8</sub> cycloalkyl)<sub>2</sub>,

hydroxymethyl, C<sub>1</sub>-C<sub>6</sub> acyl, cyano, azido, C<sub>1</sub>-C<sub>6</sub> thioalkyl,

20       C<sub>1</sub>-C<sub>6</sub> sulfinylalkyl, C<sub>1</sub>-C<sub>6</sub> sulfonylalkyl, C<sub>3</sub>-C<sub>8</sub> thiocycloalkyl,

C<sub>3</sub>-C<sub>8</sub> sulfinylcycloalkyl, C<sub>3</sub>-C<sub>8</sub> sulfonylcycloalkyl, mercapto,

C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxycarbonyl,

C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, or C<sub>2</sub>-C<sub>4</sub> alkynyl;

Z<sup>a</sup> is a bond, -CH<sub>2</sub>-, -S-, SO<sub>2</sub>, -NH-, -O-, -OCH<sub>2</sub>-, -S-CH<sub>2</sub>-, -SO<sub>2</sub>-, or

25       -CH<sub>2</sub>CH<sub>2</sub>-;

R<sup>77</sup> is phenyl, substituted phenyl, or a 5- to 10-membered optionally  
substituted heterocyclic aromatic ring;

-93-

$R^5$  is hydrogen, halogen,  $C_1$ - $C_6$  perfluoroalkyl, 1,1-difluoro( $C_1$ - $C_6$ )alkyl,

$C_1$ - $C_6$  alkyl,  $-(CH_2)_n$ -N-piperidinyl,  $-(CH_2)_n$ -piperazinyl,

$-(CH_2)_n$ -piperazinyl[ $N_4$ -( $C_1$ - $C_6$ )alkyl],  $-(CH_2)_n$ -N-pyrrolidyl,

$-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n$ -N-imidazolyl,  $-(CH_2)_n$ -N-morpholino,

$-(CH_2)_n$ -N-thiomorpholino,  $-C=CH_2$ ,  $-CH=CH-(C_1-C_6)$ alkyl,



$-(CH_2)_n$ -N-hexahydroazepine,  $-(CH_2)_nNH_2$ ,  $-(CH_2)_nNH$

( $C_1$ - $C_6$ alkyl),  $-(CH_2)_nN(C_1-C_6alkyl)_2$ , -1-oxo( $C_1$ - $C_6$ )alkyl,

carboxy, ( $C_1$ - $C_6$ )alkyloxycarbonyl, N-( $C_1$ - $C_6$ )alkylcarbamoyl,

phenyl or substituted phenyl, wherein the substituted phenyl can

have from one to three substituents independently selected from

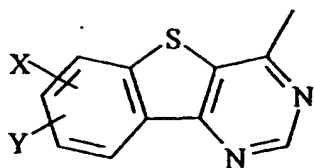
$E^1$ ,  $E^2$ ,  $E^3$  or a monocyclic heteroaryl group, and each  $C_1$ - $C_6$  alkyl

group can be substituted with  $-OH$ ,  $-NH_2$  or  $-NAB$ , where A and B

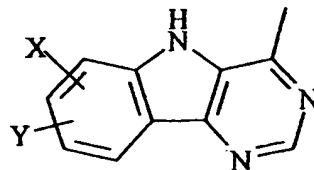
are as defined above; and

n is 1 to 4, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

23. A compound of Claim 22 wherein Q is

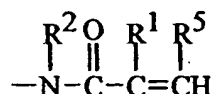


24. A compound of Claim 22 wherein Q is

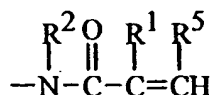


-94-

25. A compound of Claim 23 wherein X is



26. A compound of Claim 24 wherein X is



- 5      27. A pharmaceutically acceptable composition that comprises a compound of Claim 1.
28. A pharmaceutically acceptable composition that comprises a compound of Claim 13.
- 10      29. A pharmaceutically acceptable composition that comprises a compound of Claim 22.
30. A method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Claim 1.
- 15      31. A method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis a therapeutically effective amount of a compound of Claim 1.
32. A method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Claim 13.
- 20      33. A method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis a therapeutically effective amount of a compound of Claim 13.



-95-

34. A method of treating cancer, the method comprising administering to a patient having cancer a therapeutically effective amount of a compound of Claim 22.
- 5 35. A method of treating or preventing restenosis, the method comprising administering to a patient having restenosis or at risk of having restenosis, a therapeutically effective amount of a compound of Claim 22.
36. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient a tyrosine kinase inhibition a tyrosine kinase inhibiting amount of a compound of Claim 1.
- 10 37. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient in need of tyrosine kinase inhibition a amount of tyrosine kinase inhibiting amount of a compound of Claim 13.
- 15 38. A method of irreversibly inhibiting tyrosine kinases, the method comprising administering to a patient in need of tyrosine kinase inhibition a tyrosine kinase inhibiting amount of a compound of Claim 22.
39. A method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Claim 1.
- 20 40. A method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Claim 13.
41. A method of treating psoriasis, the method comprising administering to a patient having psoriasis a therapeutically effective amount of a compound of Claim 22.

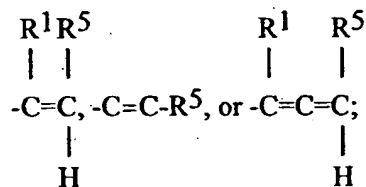
-96-

42. A method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Claim 1.
43. A method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Claim 13.
44. A method of treating atherosclerosis, the method comprising administering to a patient having atherosclerosis a therapeutically effective amount of a compound of Claim 22.
45. A method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Claim 1.
46. A method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Claim 13.
47. A method of treating endometriosis, the method comprising administering to a patient having endometriosis a therapeutically effective amount of a compound of Claim 22.
48. A compound according to Claim 1 wherein X is -D-E-F and F is
- $$\begin{array}{ccc}
 R^1 & R^5 & \\
 | & | & \\
 -C=C, & -C=C-R^5, & \text{or } -C=C=C; \\
 | & & | \\
 H & & H
 \end{array}$$
- and  $R^5$  is 1,1-difluoro( $C_1$ - $C_6$ )alkyl,  $C_1$ - $C_6$  alkyl,  $-(CH_2)_n$ -N-piperidinyl,  $-(CH_2)_n$ -piperazinyl,  $-(CH_2)_n$ -piperazinyl[N<sub>4</sub>-( $C_1$ - $C_6$ )alkyl],  $-(CH_2)_n$ -N-pyrrolidyl,  $-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n$ -N-imidazolyl,

-97-

$-(CH_2)_n$ -N-morpholino,  $-(CH_2)_n$ -N-thiomorpholino,  
 $-CH=CH-(C_1-C_6)$ alkyl,  $-(CH_2)_n$ -N-hexahydroazepine,  
 $-(CH_2)_n$ NH<sub>2</sub>,  $-(CH_2)_n$ NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  $-(CH_2)_n$ N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>,  
 $-1$ -oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl,  
 5 N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, and each C<sub>1</sub>-C<sub>1</sub> alkyl group of  
 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl,  $-CH=CH-(C_1-C_6)$ alkyl,  
 $-1$ -oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, or  
 $-N-(C_1-C_6)$ alkylcarbamoyl is substituted with -OH, -NH<sub>2</sub>, or  
 $-NAB$ , where A and B are as defined above; or

10 Y is -D-E-F and F is



15

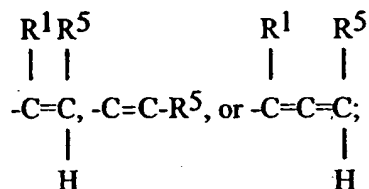
and R<sup>5</sup> is 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl,  $-(CH_2)_n$ -N-piperidinyl,

$-(CH_2)_n$ -piperazinyl,  $-(CH_2)_n$ -piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],  
 $-(CH_2)_n$ -N-pyrrolidyl,  $-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n$ -N-imidazolyl,  
 $-(CH_2)_n$ -N-morpholino,  $-(CH_2)_n$ -N-thiomorpholino,  
 20  $-CH=CH-(C_1-C_6)$ alkyl,  $-(CH_2)_n$ -N-hexahydroazepine,  
 $-(CH_2)_n$ NH<sub>2</sub>,  $-(CH_2)_n$ NH(C<sub>1</sub>-C<sub>6</sub> alkyl),  $-(CH_2)_n$ N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>,  
 $-1$ -oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl,  
 N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, and each C<sub>1</sub>-C<sub>1</sub> alkyl group of  
 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl,  $-CH=CH-(C_1-C_6)$ alkyl,  
 25  $-1$ -oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, or  
 $-N-(C_1-C_6)$ alkylcarbamoyl is substituted with -OH, -NH<sub>2</sub>, or  
 $-NAB$ , where A and B are as defined above.

25

-98-

49. A compound according to Claim 13 wherein X is -D-E-F and F is



and R<sup>5</sup> is 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,

-(CH<sub>2</sub>)<sub>n</sub>-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],

-(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine,

-(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>

alkyl)<sub>2</sub>, -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl,

N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbonyl, and each C<sub>1</sub>-C<sub>1</sub> alkyl group of

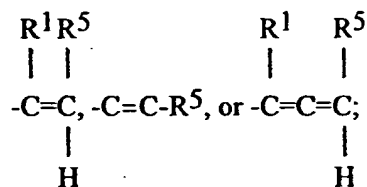
1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

-1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, or

-N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbonyl is substituted with -OH, -NH<sub>2</sub>, or

-NAB, where A and B are as defined above; or

Y is -D-E-F and F is



and R<sup>5</sup> is 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,

-(CH<sub>2</sub>)<sub>n</sub>-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],

-(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine,

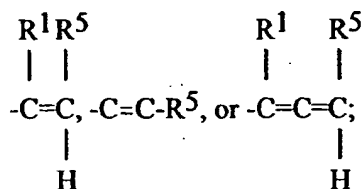
-(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub>

alkyl)<sub>2</sub>, -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl,

-99-

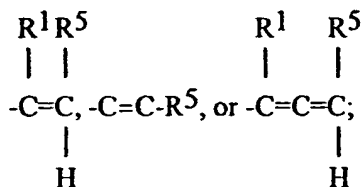
N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, and each C<sub>1</sub>-C<sub>1</sub> alkyl group of  
 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, or  
 -N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl is substituted with -OH, -NH<sub>2</sub>, or  
 -NAB, where A and B are as defined above.

50. A compound according to Claim 22 wherein X is -D-E-F and F is



and R<sup>5</sup> is 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],  
 -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,  
 -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine,  
 -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>,  
 -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl,  
 N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, and each C<sub>1</sub>-C<sub>1</sub> alkyl group of  
 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, or  
 -N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl is substituted with -OH, -NH<sub>2</sub>, or  
 -NAB, where A and B are as defined above; or

Y is -D-E-F and F is



-100-

and R<sup>5</sup> is 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl, -(CH<sub>2</sub>)<sub>n</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl],  
 -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl, -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,  
 5 -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl, -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine,  
 -(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>n</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>,  
 -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl,  
 N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl, and each C<sub>1</sub>-C<sub>1</sub> alkyl group of  
 1,1-difluoro(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -CH=CH-(C<sub>1</sub>-C<sub>6</sub>)alkyl,  
 10 -1-oxo(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyloxycarbonyl, or  
 -N-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl is substituted with -OH, -NH<sub>2</sub>, or  
 -NAB, where A and B are as defined above.

51. A compound according to Claim 1 wherein X is -D-E-F;

Y is -SR<sup>4</sup>, -OR<sup>4</sup>, or -NHR<sup>3</sup>;

15 and R<sup>3</sup> and R<sup>4</sup> are -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,  
 -(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,  
 -(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein

20

A  
|

the substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are  
 independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

25

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

or

Y is -D-E-F;

-101-

X is  $-SR^4$ ,  $-OR^4$ , or  $-NHR^3$ ;

and  $R^3$  and  $R^4$  are  $-(CH_2)_n-N$ -piperidinyl,  $-(CH_2)_n-N$ -piperazinyl,

$-(CH_2)_n-N_1$ -piperazinyl[ $N_4-(C_1-C_6)$ alkyl],  $-(CH_2)_n-N$ -pyrrolidyl,

$-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n-N$ -imidazolyl,  $-(CH_2)_n$ -imidazolyl,

5  $-(CH_2)_n-N$ -morpholino,  $-(CH_2)_n-N$ -thiomorpholino,

$-(CH_2)_n-N$ -hexahydroazepine or substituted  $C_1-C_6$  alkyl, wherein

A

|

the substituents are selected from  $-OH$ ,  $-NH_2$ , or  $-N-B$ , A and B are

10 independently hydrogen,  $C_1-C_6$  alkyl,  $-(CH_2)_nOH$ ,

$-(CH_2)_n-N$ -piperidinyl,  $-(CH_2)_n-N$ -piperazinyl,

$-(CH_2)_n-N_1$ -piperazinyl[ $N_4-(C_1-C_6)$ alkyl],  $-(CH_2)_n-N$ -pyrrolidyl,

$-(CH_2)_n-N$ -pyridyl,  $-(CH_2)_n$ -imidazolyl, or  $-(CH_2)_n-N$ -imidazolyl.

52. A compound according to Claim 13 wherein X is  $-D-E-F$ ;

15 Y is  $-SR^4$ ,  $-OR^4$ , or  $-NHR^3$ ;

and  $R^3$  and  $R^4$  are  $-(CH_2)_n-N$ -piperidinyl,  $-(CH_2)_n-N$ -piperazinyl,

$-(CH_2)_n-N_1$ -piperazinyl[ $N_4-(C_1-C_6)$ alkyl],  $-(CH_2)_n-N$ -pyrrolidyl,

$-(CH_2)_n$ -pyridinyl,  $-(CH_2)_n-N$ -imidazolyl,  $-(CH_2)_n$ -imidazolyl,

$-(CH_2)_n-N$ -morpholino,  $-(CH_2)_n-N$ -thiomorpholino,

20  $-(CH_2)_n-N$ -hexahydroazepine or substituted  $C_1-C_6$  alkyl, wherein

-102-

A  
|the substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B areindependently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

5

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

or

Y is -D-E-F;

10

X is -SR<sup>4</sup>, -OR<sup>4</sup>, or -NHR<sup>3</sup>;and R<sup>3</sup> and R<sup>4</sup> are -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,-(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

15

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, whereinA  
|the substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B areindependently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

20

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl.

53. A compound according to Claim 22 wherein X is -D-E-F;

Y is -SR<sup>4</sup>, -OR<sup>4</sup>, or -NHR<sup>3</sup>;

25

and R<sup>3</sup> and R<sup>4</sup> are -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,-(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,



-103-

-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein

A  
|

5 the substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl;

10 or

Y is -D-E-F;

X is -SR<sup>4</sup>, -OR<sup>4</sup>, or -NHR<sup>3</sup>;

and R<sup>3</sup> and R<sup>4</sup> are -(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

15 -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-morpholino, -(CH<sub>2</sub>)<sub>n</sub>-N-thiomorpholino,

-(CH<sub>2</sub>)<sub>n</sub>-N-hexahydroazepine or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, wherein

A  
|

20 the substituents are selected from -OH, -NH<sub>2</sub>, or -N-B, A and B are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>n</sub>OH,

-(CH<sub>2</sub>)<sub>n</sub>-N-piperidinyl, -(CH<sub>2</sub>)<sub>n</sub>-N-piperazinyl,

-(CH<sub>2</sub>)<sub>n</sub>-N<sub>1</sub>-piperazinyl[N<sub>4</sub>-(C<sub>1</sub>-C<sub>6</sub>)alkyl], -(CH<sub>2</sub>)<sub>n</sub>-N-pyrrolidyl,

-(CH<sub>2</sub>)<sub>n</sub>-N-pyridyl, -(CH<sub>2</sub>)<sub>n</sub>-imidazolyl, or -(CH<sub>2</sub>)<sub>n</sub>-N-imidazolyl.

25 54. The compounds:

N-[4-(6-Bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]acrylamide;

30 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylamide;

-104-

N-[4-(7-Chloro-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]propynamide;

5 N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]propynamide;

10 N-[4-(7-Trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)quinazolin-7-yl]propynamide;

N-[4-(4-6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-ynamide;

15 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

N-[4-(6-Bromo-5-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]buta-2,3-dienamide;

20 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

25 N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacryl-amide;

30 N-[4-(6-Nitro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)quinazoline;

-105-

6-(S-Vinylsulfonamido)-4-(6-pyrrol-1-yl-2,3-dihydroindol-1-yl)quinazoline;

N-[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

5 N-[4-(6-Pyrrol-1-yl-2,3-dihydroindol-1-yl)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylamide

N-[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide;

10 N-[4-(Octahydroindol-1-yl)-7-[3-(4-morpholino)propoxy]-quinazolin-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

N-[4-(Octahydroindol-1-yl)quinazolin-6-yl]-4-oxopent-2-enamide;

15 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

20 N-[4-(6,7-Dihydro-5H-[1,3]dioxolo[4,5-f]indol-5-yl)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

25 N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

30 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

-106-

N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

5 N-[4-(6-Azido-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

10 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(5-benzyloxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

Pent-2-enedioic acid 1 {[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

15 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(5-Methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

20 7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(5-methoxy-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]amide;

25 4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]amide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

30 N-[4-(2,3,4,5-Tetrahydro-1H-benzoazepin-1-yl)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

-107-

N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

5 N-[4-(5-Hydroxy-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

10 N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(5-Amino-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

15 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]-pyrimid-6-yl]buta-2,3-dienamide;

20 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(1,2,3,4,5,6-Hexahydrobenzo[b]azocin-1-yl)pyrido[3,4-d]-pyrimid-6-yl]but-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

25 N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]-pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

30 N-[4-(6-Fluoro-7-methyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]-pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(6-chloro-2,3-dihydroindol-1-yl)-pyrido[3,4-d]pyrimidine;

-108-

6-(S-Vinylsulfonamido)-4-(2,3,6,7,8,9-hexahydro-1H-benzo[g]indol-1-yl) pyrido[3,4-d]pyrimidine;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

5 N-[4-(2,3,6,7,8,9-Hexahydro-1H-benzo[g]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

10 N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

15 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

20 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

25 N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

30 N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-Ethynyl-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(2,3-dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

5 Pent-2-enedioic acid 1 {[4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(6-Chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

10 N-[4-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

15 4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2,3,5,6-tetrahydropyrrolo[2,3-f]indol-1-yl)pyrido[3,4-d]pyrimid-6-yl]amide;

20 N-[4-(6-Chloro-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

N-[4-(6-Ethynyl-2,3-dihydroindol-1-yl)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

25 [4-(2,3,5,6-Tetrahydropyrrolo[2,3-f]indol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)quinazolin-7-yl]acrylate;

[7-[3-(4-Morpholino)propoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

30 [4-(2,3-Dihydropyrrolo[2,3-f]indol-7-yl)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylate;

-110-

[7-[4-(N,N-dimethylamino)butoxy]-4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylate;

[4-(6-Ethynyl-2,3-dihydroindol-1-yl)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl] acrylate;

5 N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(2,3,4,5-tetrahydro-1H-benzoazepin-1-yl)quinazolin-6-yl]-4-oxobut-2-enamide;

10 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(6-bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1 {[4-(6-methyl-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

15 Pent-2-enedioic acid 1 {[4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl] ester} 5-[(3-morpholin-4-ylpropyl)amide];

[4-(6-Chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

20 [4-(6-Fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

7-Morpholin-4-ylhept-2-ynoic acid [4-(6-chloro-7-fluoro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

25 4-Morpholin-4-ylbut-2-ynoic acid [4-(6-chloro-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(6-ethynyl-2,3-dihydroindol-1-yl)quinazolin-6-yl]ester;

N-[4-(Quinol-2-ylamino)quinazolin-6-yl]acrylamide;

30 N-[4-(Indol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(Quinol-2-ylamino)quinazolin-7-yl]acrylamide;

N-[4-(Indol-5-ylamino)quinazolin-7-yl]acrylamide;



-111-

- 5 N-[4-(Quinol-3-ylamino)quinazolin-6-yl]propynamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]propynamide;  
N-[4-(Quinol-3-ylamino)quinazolin-7-yl]propynamide;  
N-[4-(Indol-5-ylamino)quinazolin-7-yl]propynamide;  
N-[4-(Quinol-5-ylamino)quinazolin-6-yl]but-2-ynamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-ynamide;  
N-[4-(Quinol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]buta-2,3-dienamide;  
N-[4-(Quinol-6-ylamino)quinazolin-6-yl]but-2-enamide;  
10 N-[4-(Indol-5-ylamino)quinazolin-6-yl]but-2-enamide;  
N-[4-(Quinol-6-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-2-enamide;  
15 N-[4-(Quinol-7-ylamino)quinazolin-6-yl]-3-chloroacrylamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]-3-chloroacrylamide;  
6-(S-Vinylsulfonamido)-4-(quinol-7-ylamino)quinazoline;  
6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)quinazoline;  
N-[7-[3-(4-Morpholino)propoxy]-4-(quinol-8-ylamino)quinazolin-  
20 6-yl]acrylamide;  
N-[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]-quinazolin-6-yl]acrylamide;  
N-[7-[4-(N,N-dimethylamino)butoxy]-4-(quinol-8-ylamino)-quinazolin-6-yl]acrylamide;  
25 N-[4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylamide;  
N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;  
N-[4-(Isoquinol-1-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-  
30 enamide;  
N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

-112-

N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

5 N-[4-(Isoquinol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)-propoxy)-4-oxobut-2-enamide;

10 N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indol-4-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

15 N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indol-6-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

20 N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-6-ylamino)quinazolin-6-yl]amide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;

25 Pent-2-enedioic acid 1 {[4-(indol-5-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-yl)propyl]amide];

Pent-2-enedioic acid 1 {[4-(1H-indazol-6-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-yl)propyl]amide];

30 N-[4-(1H-Indazol-6-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

-113-

7-Morpholin-4-ylhept-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)quinazolin-6-yl]amide;

5 4-Morpholin-4-ylbut-2-ynoic acid [4-(1H-indazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(4-benzyloxyphenylamino)-quinazolin-6-yl]amide;

10 N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(1H-Indazol-4-ylamino)pyrido[4,3-d]pyrimid-7-yl]acrylamide;

N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

15 N-[4-(1H-Indazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

20 N-[4-(Indol-5-ylamino)pyrido[4,3-d]pyrimid-7-yl]propynamide;

N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

25 N-[4-(1H-Benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

30 N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

-114-

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1H-Benzotriazol-7-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

5 N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

6-(S-Vinylsulfonamido)-4-(benzothiazol-5-ylamino)pyrido[3,4-d]-pyrimidine;

10 6-(S-Vinylsulfonamido)-4-(indol-5-ylamino)pyrido[3,4-d]-pyrimidine;

N-[4-(Benzothiazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-oxopent-2-enamide;

15 N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

20 N-[4-(Benzothiazol-6-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

25 N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indan-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

30 N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

-115-

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(Indan-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

5 N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

10 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

15 Pent-2-enedioic acid 1 {[4-(1,2,3,4-tetrahydronaphth-1-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1,2,3,4-Tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

N-[4-(Indol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

20 7-Morpholin-4-ylhept-2-ynoic acid [4-(1,2,3,4-tetrahydronaphth-2-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)-pyrido[3,4-d]pyrimid-6-yl]amide;

25 4-Morpholin-4-ylbut-2-ynoic acid [4-(benzo[c][2,1,3]thiadiazol-4-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)-pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(Benzo[c][2,1,3]thiadiazol-4-ylamino)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

30 N-[4-(Indol-5-ylamino)benzo[b]thieno[3,2-d]pyrimid-6-yl]acrylamide;

[4-(Benzimidazol-5-ylamino)quinazolin-6-yl]acrylate;

-116-

- [4-(Indol-5-ylamino)quinazolin-6-yl]acrylate;  
[4-(Benzimidazol-5-ylamino)quinazolin-7-yl]acrylate;  
[4-(Indol-5-ylamino)quinazolin-7-yl]acrylate;  
[7-[3-(4-Morpholino)propoxy]-4-(benzimidazol-5-ylamino)-  
5 quinazolin-6-yl]acrylate;  
[4-(Indol-5-ylamino)-7-[4-(N,N-dimethylamino)butoxy]-  
quinazolin-6-yl]acrylate;  
[7-[4-(N,N-dimethylamino)butoxy]-4-(6-methoxyquinol-8-  
ylamino)quinazolin-6-yl]acrylate;  
10 [4-(Indol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-  
yl]acrylate;  
N-(3-(4-Morpholino)propylamino)-4,O-[4-(6-methoxyquinol-8-  
ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;  
N-(3-(4-Morpholino)propylamino)-4,O-[4-(indol-5-ylamino)-  
15 quinazolin-6-yl]-4-oxobut-2-enamide;  
4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(1-methylindol-  
5-ylamino)quinazolin-6-yl]ester;  
4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(indol-5-  
ylamino)quinazolin-6-yl]ester;  
20 Pent-2-enedioic acid 1 {[4-(indol-5-ylamino)quinazolin-6-yl]ester}  
5-[(3-morpholin-4-ylpropyl)amide];  
Pent-2-enedioic acid 1 {[4-(1-methylindol-5-ylamino)quinazolin-6-  
yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];  
[4-(2-Methylindol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-  
25 yl)propylthio)but-2-enoate;  
[4-(Indol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)-  
propylthio)but-2-enoate;  
7-Morpholin-4-ylhept-2-ynoic acid [4-(3-cyanoindol-5-ylamino)-  
quinazolin-6-yl]ester;  
30 7-Morpholin-4-ylhept-2-ynoic acid [4-(indol-5-ylamino)-  
quinazolin-6-yl]ester;

-117-

4-Morpholin-4-ylbut-2-ynoic acid [4-(benzothien-5-ylamino)-  
quinazolin-6-yl]ester;

4-Morpholin-4-ylbut-2-ynoic acid [4-(indol-5-ylamino)quinazolin-  
6-yl]ester;

5 N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-6-  
yl]acrylamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-7-yl]acrylamide;

10 N-[4-(2-Benzylbenzimidazol-5-ylamino)quinazolin-7-  
yl]acrylamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-  
yl]propynamide;

N-[4-(1-Benzylbenzindazol-5-ylamino)quinazolin-6-  
yl]propynamide;

15 N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-  
yl]propynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-7-  
yl]propynamide;

20 N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]but-2-  
ynamide;

N-[4-(1-Phenylsulfonylindol-5-ylamino)quinazolin-6-yl]buta-2,3-  
dienamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]but-2-enamide;

25 N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4,4,4-  
trifluorobut-2-enamide;

N-[4-(1-Benzylindol-5-ylamino)quinazolin-6-yl]-4,4,4-trifluorobut-  
2-enamide;

N-[4-(1-Benzylindol-6-ylamino)quinazolin-6-yl]-3-  
chloroacrylamide;

30 6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-  
ylamino)quinazoline;

-118-

N-[7-[3-(4-Morpholino)propoxy]-4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylamide;

N-[4-(1-Benzylindol-6-ylamino)-7-[4-(N,N-dimethylamino)butoxy]quinazolin-6-yl]acrylamide;

5 N-[4-(2-Phenylbenzimidazol-5-ylamino)-7-[3-(4-morpholino)propoxy]quinazolin-6-yl]acrylamide;

N-[4-(2-Phenylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-oxopent-2-enamide;

10 N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(3-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-ethoxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propoxy)-4-oxobut-2-enamide;

15 N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

20 N-[4-(1-Benzylbenzimidazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(42-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

25 N-[4-(2-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

30 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];



-119-

Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

5 N-[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(1-Benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

10 4-Morpholin-4-ylbut-2-ynoic acid [4-(3-benzylbenzotriazol-5-ylamino)quinazolin-6-yl]amide;

4-Morpholin-4-ylbut-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

15 N-[4-(3-Benzylbenzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]acrylamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

20 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]propynamide;

N-[4-(2-{Pyrid-2-yl}benzotriazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-ynamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]buta-2,3-dienamide;

25 N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]but-2-enamide;

N-[4-(2-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

30 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4,4,4-trifluorobut-2-enamide;

N-[4-(1-Phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-3-chloroacrylamide;

-120-

6-(S-Vinylsulfonamido)-4-(1-phenethylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimidine;

6-(S-Vinylsulfonamido)-4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimidine;

5 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-hydroxy-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(N,N-dimethylamino)propylamino)-4-oxobut-2-enamide;

10 N-[4-(2-Benzyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propoxy)-4-oxobut-2-enamide;

N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

15 N-[4-(2-Benzyloxyindol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(4-morpholino)propylamino)-4-oxobut-2-enamide;

4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzyloxybenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

20 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

25 Pent-2-enedioic acid 1 {[4-(2-benzylsulfonylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide} 5-[(3-morpholin-4-ylpropyl)amide];

N-[4-(4-benzyloxybenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

30 N-[4-(2-Benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enamide;

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

-121-

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylsulfonylbenzimidazol-5-ylamino)pyrido[3,4-d]pyrimid-6-yl]amide;

N-[4-(2-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

5 N-[4-(1-Benzylbenzindazol-5-ylamino)benzo[b]thieno[3,2-d]-pyrimid-6-yl]acrylamide;

[4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]acrylate;

N-(3-(4-Morpholino)propylamino)-4,O-[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-oxobut-2-enamide;

10 4,4-Difluoro-8-(morpholin-4-yl)oct-2-enoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester;

Pent-2-enedioic acid 1 {[4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester} 5-[(3-morpholin-4-ylpropyl)amide];

15 [4-(2-Benzylbenzindazol-5-ylamino)quinazolin-6-yl]-4-(3-(morpholin-4-yl)propylthio)but-2-enoate; and

7-Morpholin-4-ylhept-2-ynoic acid [4-(2-benzylbenzindazol-5-ylamino)quinazolin-6-yl]ester.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/15592

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/04 A61K31/505 C07D401/04 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 0 837 063 A (PFIZER) 22 April 1998 see claim 1	1-12
P,Y	WO 97 38983 A (WARNER LAMBERT CO ;BRIDGES ALEXANDER JAMES (US); DENNY WILLIAM ALE) 23 October 1997 see claim 1	1-12
Y	WO 97 22596 A (ZENECA LTD ;ZENECA PHARMA SA (FR); LOHMANN JEAN JACQUES MARCEL (FR) 26 June 1997 see claim 1	1-12
Y	WO 96 09294 A (WELLCOME FOUND ;HUDSON ALAN THOMAS (GB); VILE SADIE (GB); BARRACLO) 28 March 1996 see claim 1	1-12
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"B" document member of the same patent family

Date of the actual completion of the international search

23 September 1998

Date of mailing of the international search report

15.01.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax: (+31-70) 340-3016

Authorized officer

GETTINS M.P.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/15592

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 475 001 A (BARKER ANDREW J) 12 December 1995 cited in the application see claim 1 ---	1-12
Y	US 5 457 105 A (BARKER ANDREW J) 10 October 1995 cited in the application see claim 1 ---	1-12
Y	WO 95 23141 A (PFIZER ;ARNOLD LEE D (US)) 31 August 1995 cited in the application see claim 1 ---	1-12
Y	WO 95 19774 A (WARNER LAMBERT CO) 27 July 1995 cited in the application see claim 1 ---	1-12
Y	EP 0 602 851 A (ZENECA LTD) 22 June 1994 see claim 1 ---	1-12
Y	WO 95 15758 A (HSU CHIN YI JENNY ;ZILBERSTEIN ASHER (US); JOHNSON SUSAN E (US); M) 15 June 1995 Formula I see page 4 -----	1-12

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 15592

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 30 - 47  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 30-47 are directed to a method of treatment of the human/  
animal body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13, 27, 30, 31, 36, 39, 42, 45, 48, 51, 54 (part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13,27,30,31,36,39,42,45,48,51,54 (part)

Compounds I

2. Claims: 13(part),14,21 (both complete),28,32,33,37,40,43, 46,49,52 (all partial)

Compounds II where Q is as in claim 14.

3. Claims: 13(part),15,18 (both complete),28,32,33,37,40,43, 46,49,52 (all partial)

Compounds II where Q is as in claim 15

4. Claims: 13(part),16,19,20 (all complete),28,32,33,37,40,43, 46,49,52,54 (all partial)

Compounds II where Q is as in claim 16

5. Claims: 13(part),17 (complete),28,32,33,37,40,43,46,49,52, 54 (all partial)

Compounds II where Q is as in claim 17

6. Claims: 22(part),23,25 (both complete), 29,34,35,38,41,44, 47,50,53, 54 (all part)

Compounds III where Q is as in claim 23.

7. Claims: 22(part),24,26 (both complete), 29,34,35,38,41,44, 47,50,53, 54 (all part)

Compounds III where Q is as in claim 24

8. Claims: 22,29,34,35,38,41,44,47,50,53, 54 (all part)

Compounds III where Q is the pyrimidoindole not covered by claim 24.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 22,29,34,35,38,41,44,47,50,53, 54 (all part)

Compounds III where Q is the quinazolinopyrrolo ring



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/15592

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0837063	A	22-04-1998	CA 2218945 A		17-04-1998
			JP 10152477 A		09-06-1998
-----					
WO 9738983	A	23-10-1997	AU 2446397 A		07-11-1997
-----					
WO 9722596	A	26-06-1997	AU 1106197 A		14-07-1997
			CZ 9801882 A		16-09-1998
			EP 0873319 A		28-10-1998
			NO 982784 A		17-08-1998
-----					
WO 9609294	A	28-03-1996	AU 3482495 A		09-04-1996
			EP 0782570 A		09-07-1997
			JP 10505600 T		02-06-1998
-----					
US 5475001	A	12-12-1995	AU 7191694 A		20-02-1995
			EP 0635498 A		25-01-1995
			WO 9503283 A		02-02-1995
			JP 9500636 T		21-01-1997
			ZA 9405156 A		19-01-1995
-----					
US 5457105	A	10-10-1995	US 5616582 A		01-04-1997
			AT 130000 T		15-11-1995
			AU 661533 B		27-07-1995
			AU 3101093 A		22-07-1993
			CA 2086968 A,C		21-07-1993
			CZ 282038 B		16-04-1997
			DE 69300754 D		14-12-1995
			DE 69300754 T		28-03-1996
			DK 566226 T		18-03-1996
			EP 0566226 A		20-10-1993
			ES 2078798 T		16-12-1995
			FI 930208 A		21-07-1993
			GR 3018143 T		29-02-1996
			HK 36497 A		04-04-1997
			HU 9500185 A		28-07-1995
			MX 9300277 A		30-06-1994
			NO 301541 B		10-11-1997
			NZ 245662 A		26-09-1995
			SK 1693 A		09-09-1993
			ZA 9300015 A		20-07-1993
			JP 6073025 A		15-03-1994
-----					
WO 9523141	A	31-08-1995	AU 686843 B		12-02-1998
			AU 2972795 A		11-09-1995
			BR 9506936 A		09-09-1997
			CA 2183655 A		31-08-1995
			CN 1141633 A		29-01-1997
			CZ 9602413 A		16-07-1997
			EP 0746554 A		11-12-1996
			FI 963283 A		22-08-1996
			HU 76291 A		28-07-1997
			JP 9501953 T		25-02-1997
			NO 963506 A		22-10-1996
			NZ 278135 A		25-03-1998
			PL 315941 A		09-12-1996
			US 5736534 A		07-04-1998
-----					
WO 9519774	A	27-07-1995	US 5654307 A		05-08-1997

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/15592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519774 A		AU 686334 B	05-02-1998
		AU 1731495 A	08-08-1995
		AU 686339 B	05-02-1998
		AU 1833495 A	08-08-1995
		BG 100614 A	31-03-1997
		BG 100615 A	28-02-1997
		CA 2177372 A	27-07-1995
		CA 2177392 A	27-07-1995
		CN 1139383 A	01-01-1997
		CN 1139430 A	01-01-1997
		CZ 9601970 A	17-09-1997
		CZ 9601971 A	16-07-1997
		EP 0742717 A	20-11-1996
		EP 0741711 A	13-11-1996
		FI 962855 A	13-09-1996
		FI 962856 A	25-09-1996
		HR 950033 A	31-10-1997
		HR 950034 A	31-10-1997
		HU 74590 A	28-01-1997
		HU 74589 A	28-01-1997
		JP 9508126 T	19-08-1997
		JP 9508127 T	19-08-1997
		MD 960211 A	30-04-1998
		MD 960217 A	30-04-1998
		NO 963093 A	24-07-1996
		NO 963094 A	24-07-1996
		PL 315632 A	25-11-1996
		PL 315633 A	25-11-1996
		SK 89496 A	08-10-1997
		SK 89596 A	06-08-1997
		WO 9519970 A	27-07-1997
		US 5679683 A	21-10-1997
		ZA 9500441 A	10-10-1995
		ZA 9500440 A	10-10-1995
EP 0602851 A	22-06-1994	AT 143956 T	15-10-1996
		AU 664496 B	16-11-1995
		AU 5072893 A	23-06-1994
		CA 2103383 A	11-06-1994
		CN 1094043 A	26-10-1994
		CZ 9302651 A	15-06-1994
		DE 69305310 D	14-11-1996
		DE 69305310 T	13-02-1997
		DK 602851 T	24-03-1997
		ES 2093367 T	16-12-1996
		FI 935431 A	11-06-1994
		GR 3021326 T	31-01-1997
		HU 65622 A	28-07-1994
		JP 6336481 A	06-12-1994
		MX 9307778 A	29-07-1994
		NO 934504 A	13-06-1994
		NZ 250218 A	25-06-1996
		US 5580870 A	03-12-1996
		ZA 9308594 A	10-06-1994
WO 9515758 A	15-06-1995	US 5480883 A	02-01-1996
		US 5710158 A	20-01-1998
		AU 1305095 A	27-06-1995

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 98/15592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515758 A		EP 0871448 A	21-10-1998
		US 5795889 A	18-08-1998
		US 5646153 A	08-07-1997
		US 5721237 A	24-02-1998
		US 5714493 A	03-02-1998
-----			